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ATMP & Orphan Diseases: Data sources beyond RCTs

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Goals of the plattform

Since the introduction of AMNOG in 2011, Germany has a well-established and widely accepted „adaptive system" for the assessment of the patient-relevant additional benefit (Health Technology Assessment, HTA). The assessment of the additional benefit by the Federal Joint Committee (G-BA) is the result of expert work based on a law (AMNOG) and procedural and methodical regulations.

The active players on the side of the G-BA and the health insurance funds are classified as scientists, hospital physicians and office-based statutory health insurance physicians, the Medical Service of the Health Funds and employees of the insurance fund administration, but also as patient representatives, however, they act on the basis of their own interests. Value dossiers for new pharmaceuticals, likewise qualified and interest-based, are submitted to the G-BA by the pharmaceutical companies, which serve as the basis for the assessment of the additional benefit.

Because the supply of pharmaceuticals to the population is significantly influenced by the assessment of the additional benefit, it makes sense to provide critical and careful support for the assessment process with a focus on identifying possible faults and counteracting imbalances. The Interdisciplinary Platform on Benefit Assessment set itself the task of supporting the benefit assessment within a small group of experts with the following objectives:

Discussing the procedures for the assessment of the additional benefit, including in relation to approval of pharmaceuticals,

Working towards international standards of evidence-based medicine and of health economy being adhered to as well as applied and further developed,

Determining whether and to what extent patient-relevant additional benefits, in particular in the areas of mortality, morbidity and quality of life, are identified and which methodological problems occur during the process,

dentifying possible undesirable developments, in particular with regard to supplying patients with new active substances,

Enabling and holding a constructive dialogue with all players involved in the benefit assessment procedure, e. g. on the further development of the legal framework conditions of AMNOG.

Moreover, the European perspective in HTA of innovative pharmaceuticals was reinforced by the European Commission's proposal for a Regulation on HTA in 2018. Monitoring the conflict between the well-established national assessment and the intended European HTA harmonisation is also a central concern of the platform. The Interdisciplinary Platform would like to make a contribution to ensuring that new active substances are transparently and fairly assessed. According to the Advisory Council, an interdisciplinary dialogue about the results of the assessment and the applied benefit assessment methods is essential. Furthermore, in the benefit assessment process it sees a good opportunity to inform the prescribing physicians of the expected additional benefits of new pharmaceuticals for patients earlier than it was previously the case.

The Interdisciplinary Platform is a result of the discussion process between clinicians and experts. The mutual desire to pool specialist knowledge in the form of interdisciplinary seminars is supported by an open consortium of sponsors. These include AbbVie Deutschland GmbH & Co. KG, DAK Gesundheit, MSD Sharp & Dohme GmbH, Novo Nordisk Pharma GmbH, Roche Pharma AG, Association of Research-Based Pharmaceutical Companies (vfa e.V.) and Cencora Global Consulting Services.

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

Assessing the benefit of advanced therapies: What could a world beyond RCTs look like?

Professor Dr Jörg Ruof

Dear readers

The assessment of benefits, pricing, and reimbursement of advanced therapy medicinal products (ATMPs) and innovations for rare diseases (orphan diseases, ODs) are central topics in the German government's ongoing pharmaceutical dialogue. This publication provides a valuable overview of the current fields of discussion. In line with the platform's objectives, the focus here is more on the scientific aspects of evidence and (additional) benefit than on the specifics of pricing mechanisms.

Across the entire pharmaceutical lifecycle, from the exploration of molecular mechanisms to the development of clinical data, manufacturing, and patient application, including pharmacokinetics and pharmacodynamics, novel therapeutic approaches such as gene therapies, cell-based therapies, or bioengineered tissue products represent a profound shift in biomedical paradigms.

This creates both opportunities and challenges for the healthcare system: opportunities to improve patient care, but also major challenges regarding the assessment of benefits and risks – as described in the introductory article by the Paul-Ehrlich-Institute (PEI) – as well as in evaluating the additional benefit relevant to HTA procedures. It appears essential that progressive and integrative methodologies complement the current HTA focus on the gold standard of RCTs in the future:

- The strength and reliability of RCT findings increase with larger patient populations. However, the trend in ATMPs, orphan drugs, and targeted therapies is toward increasingly small and diagnostically well-defined patient groups.
- The controlled conditions of RCTs can only reflect treatment outcomes over limited periods. Yet, the current trend in innovative technologies moves toward longer-lasting therapeutic effects (e.g., the claimed causal impact of one-time therapies), which cannot be fully verified within the constraints of short-term RCTs.
- A key advantage of randomised controlled trials (RCTs) is their high internal validity. The current trend reflects an accelerating pace of innovation cycles. As a result, external validity is becoming increasingly important for targeted and practice-oriented benefit assessments. A methodologically robust RCT using a comparator therapy that has already been superseded at the time of evaluation offers only limited relevance in HTA. Adaptive methodologies should therefore receive greater consideration.

The publication addresses routine practice data collection in several places, a concept intended to supplement RCT data with the external validity of real-world data (RWD). However, I tend to agree with Mr Jantschak's assessment that the instrument of routine practice data collection proves unsuitable for strengthening the evidence base needed to assess additional benefit within the AMNOG procedures.

So the question remains: how can progress be made? I would like to put forward four arguments for discussion:

- Clinical development programs should address and integrate questions of both internal and external validity at an early stage, explicitly and in sufficient detail.
- The tool of early scientific advice (e.g. within the framework of joint regulatory and HTA consultations) should be widely available, continuously developed, and actively used by manufacturers. The feasibility of appropriate study designs should be discussed early on and explicitly commented on by experts responsible for regulatory approval and HTA. It is worth noting the unfortunate fact that the Joint Scientific Consultation (JSC) instrument at the European level is still in an exploratory phase, and that the upcoming Joint Clinical Assessment (JCA) procedures are, for

the foreseeable future, being conducted without prior consultation which is an example of political misplanning that significantly complicates the targeted use of industrial research funding.

- David Sackett, one of the founding fathers of evidence-based medicine (EBM), repeatedly emphasised the concept of „best available evidence", i.e. the use of the best available evidence to optimise patient care. In the regulatory context, this involves drawing on the totality of preclinical and clinical data to assess benefit and risk. At the same time, future assessments of additional benefit should always take into account the entirety of relevant and processed comparative data. The pharmaceutical industry, IQWiG, and the G-BA must develop solutions to improve the acceptance of indirect comparisons in benefit assessment procedures, especially in light of the increasing number of PICO schemes (Patient / Intervention / Comparator / Outcome) in the European context.
- Finally, all stakeholders should regularly remind themselves that the concept of evidence-based medicine rests on three foundational pillars: i) scientific evidence or data; ii) the perspective of patients; and iii) the perspective of clinicians. The strong engagement of patients and physicians is one of the key success factors of the AMNOG process. The role of medical societies and patient organisations in the meaningful implementation of health technology assessment (HTA) cannot be overstated; a purely scientific evaluation of the data basis in HTA procedures alone can never do justice to the humanistic dimension of such processes and the associated prioritisation decisions. In this context, the EU HTA regulation also contains a structural flaw: by focusing on „individual contributors" i.e. expert perspectives that are not coordinated with the relevant medical societies; it overlooks the need for a broader, consensus-based approach.

Finally, despite our platform's benefit-focused perspective, it is important to acknowledge the broader shifts in the geopolitical landscape. Differential international pricing structures and disruptive economic developments, such as those related to the Most-Favoured-Nation principle, are creating scenarios that could significantly impair the timely availability of innovative therapies in Germany and Europe.

The already observable trend toward primary approval in the United States, with the subsequent delayed availability for the „rest of the world," is likely to intensify. A streamlined, rapid, and effective HTA process will be essential for Germany and Europe to maintain their position as innovation-friendly and competitive markets in this rapidly evolving global context, always with the aim of optimising patient care.

As always, heartfelt thanks go to all participants of the conference, to the sponsors – without whom this platform initiative would not be possible – and above all to the authors of this publication.

Warm regards

Jörg Ruof

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Perspectives of the Federal Ministry of Health (BMG) on ATMPs and rare diseases

Thomas Müller | Head of the Department „Pharmaceuticals, Medical Devices and Biotechnology“
Dr Jana Straßburger | Head of the Division „Biotechnological Innovations, Nanotechnology and Genetic Engineering“, Federal Ministry of Health (BMG)

Advanced Therapy Medicinal Products (ATMPs) reflect technological and scientific progress in pharmaceutical development to a particularly high degree. With their highly innovative care approaches, they are emblematic of a paradigm shift towards personalised pharmaceutical care. At the same time, they are associated with a wide range of new challenges for the healthcare system while offering substantial opportunities for its further development. With the genomic sequencing pilot programme (Modellvorhaben Genomsequenzierung), an important milestone has already been achieved in establishing an innovative care and research structure, particularly for patients with rare diseases, as well as for the further advancement of personalised medicine in Germany. This initiative may serve as a model for other innovative fields. In view of European and global developments, we are facing significant challenges. Within the framework of current EU initiatives and our national Pharmaceutical and Medical Technology Dialogue, we will set clear impulses for research, development and production, strengthen the competitiveness of the sector and thereby position Germany as a global innovation and manufacturing hub.

Advanced Therapy Medicinal Products (ATMPs)

Advanced Therapy Medicinal Products (ATMPs) are a distinct class of human pharmaceuticals based on genes, cells or tissues. ATMPs comprise gene therapies, somatic cell therapies and tissue-engineered products. Combined ATMPs, i.e. combinations of ATMPs and medical devices that meet specific requirements, are also classified as ATMPs.

ATMPs reflect technological and scientific progress in pharmaceutical development to a particularly high degree. Many ATMPs represent breakthrough innovations. Owing to their specific modes of action, they offer therapeutic options for diseases that have previously been difficult or impossible to treat using conventional methods, in some cases with potentially curative effects. To date, patients with oncological diseases and rare diseases have benefited in particular. At the same time, these innovative mechanisms of action introduce a new level of complexity into pharmaceutical care, especially with regard to manufacturing, logistics and administration. They pose challenges for pharmaceutical companies, healthcare professionals and competent authorities alike.

Since the ATMP Regulation entered into force at the end of 2008[1], more than thirty ATMPs have been authorised in the European Union (EU): four tissue-engineered products, five somatic cell therapies and twenty-one gene therapies. Currently, a total of twenty-one ATMPs are authorised (figure 1)[2].

The vast majority of authorised ATMPs are gene therapies (17 authorisations as of December 2025).

Chimeric antigen receptor (CAR) T-cell therapies are a prominent example of this highly innovative generation of pharmaceuticals. In this approach, a patient's own immune cells (T cells) are genetically modified ex vivo to express a

chimeric antigen receptor (CAR). This is achieved using so-called gene vectors (viral vectors), which transfer the genetic information encoding the CAR into the genome of the T cells. The modified T cells are then able to specifically recognise and destroy cancer cells. Following the first authorisation of a CAR T-cell therapy in 2018, seven CAR T-cell therapies are currently authorised in the EU for haematological and lymphatic malignancies. The treatment of various solid tumours is being investigated internationally in multiple clinical studies. In addition, initial successes have been achieved in the treatment of autoimmune diseases. Clinical trials are currently underway evaluating CAR T cells in combination therapies, as second-line treatments, and also for haemophilia.

Another highly innovative therapeutic approach is genome editing using CRISPR/Cas9. This technology enables DNA segments or individual nucleotides within a gene to be modified more rapidly and precisely by mutagenesis,


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is a licensed physician and pharmacist. He studied pharmacy and human medicine in Berlin and London. Following positions in the Department of Dermatology at Charité – Universitätsmedizin Berlin and in hospital pharmacies at the university hospitals of Erlangen and Rostock, he became Head of the Hospital Pharmacy at Rostock University Medical Centre. From 2007 to 2018, Thomas Müller served as Head of the Pharmaceuticals Department at the Federal Joint Committee (G-BA) in Berlin. In this role, he played a key part in the successful design, planning and implementation of the early benefit assessment and pricing framework for pharmaceuticals with new active substances (AMNOG) in Germany. Since 2018, he has headed Division 1 – Pharmaceuticals, Medical Devices and Biotechnology at the Federal Ministry of Health. He is also a lecturer at the University of Bonn.


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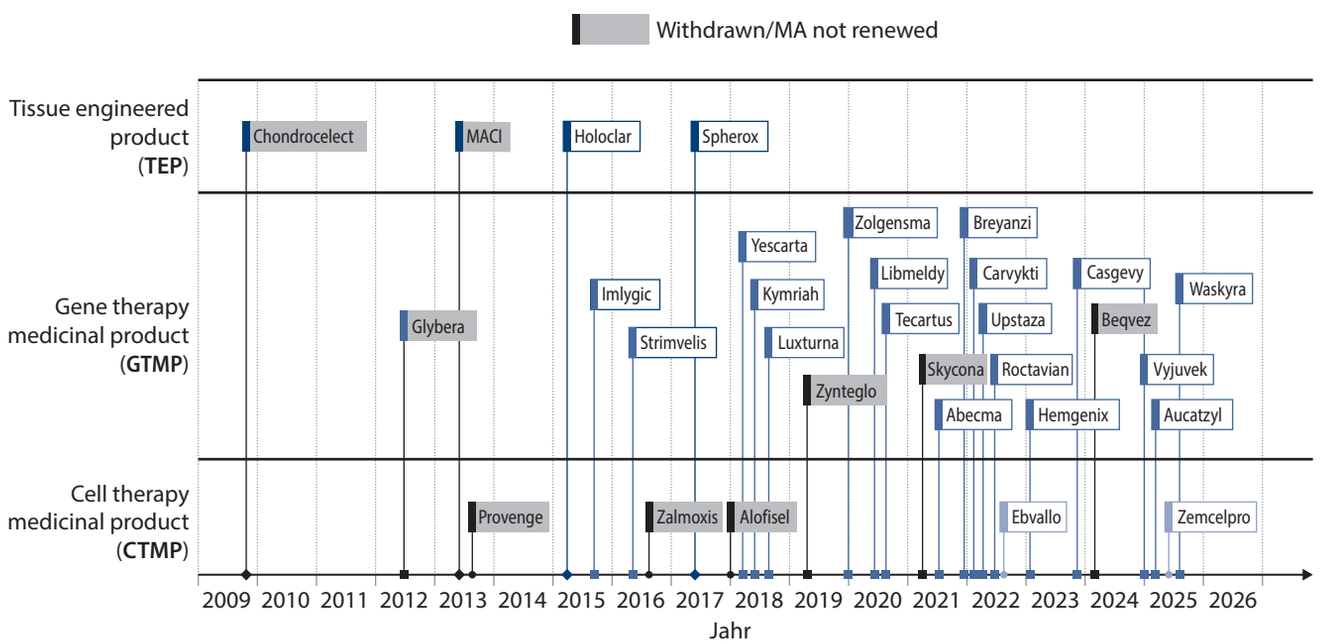
ATMP authorised since 2009



Source: CAT quarterly highlights and approved ATMPs, December 2025;
https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat

Figure 1: Since the entry into force of the ATMP Regulation at the end of 2008, more than 30 ATMP have been authorised in the European Union, including 21 gene therapies

either ex vivo or in vivo. The first EU authorisation of a CRISPR-Cas-based therapy was granted in mid-February 2024 for Casgevy® (exagamglogene autotemcel) for the treatment of sickle cell disease and beta-thalassaemia. Both conditions are rare genetic disorders of the haematopoietic system. Further therapeutic approaches currently under development target additional inherited diseases, and increasingly also cardiovascular diseases, type 2 diabetes, cancer, HIV infections and malaria[3].

The Federal Ministry of Health (BMG) closely monitors and supports developments in the ATMP field in cooperation with the Paul-Ehrlich-Institut, the federal authority responsible for biomedical pharmaceuticals. From the Ministry's perspective, this particularly concerns the regulatory, economic and infrastructural challenges that these highly innovative pharmaceuticals pose for the healthcare system.

ATMPs make a substantial contribution to the dynamism of pharmaceutical development. They have the potential to fundamentally transform existing markets and business

models, driven by high innovation pressure, and to establish new value chains. An increasing number of companies, ranging from biotech start-ups to large multinational pharmaceutical companies, are investing in ATMPs as a growth area. New business models are emerging, along with new forms of cooperation and networks.

The number of ATMPs in clinical development has been steadily increasing for years, and further innovative pharmaceutical authorisations, particularly in the field of gene therapies, are expected. This will enable a growing number of patients to access highly innovative and personalised treatment options. These therapies are typically positioned in the high-price segment. As a result, we are operating within a structural tension between the timely availability of innovative pharmaceutical therapies, while ensuring safe and quality-assured patient care, and the need to safeguard affordability within the solidarity-based system of statutory health insurance.

Progress in additional technological fields, such as artificial intelligence, advancing digitalisation, the development of new and more efficient production technologies (e.g. platform technologies), and increasing automation, will further accelerate research and development of highly innovative pharmaceuticals and open up new avenues for innovation.

Evidence generation: establishing and expanding data infrastructures

With the launch of the National Strategy for Genomic Medicine genomDE in February 2019, the Federal Ministry of Health (BMG) has pursued the objective of making the benefits of genomic medicine sustainably accessible to patients. Genomic medicine increasingly enables more precise diagnosis and treatment of diseases, as well as the implementation of individually tailored preventive measures. This personalised, genome-based approach to medicine therefore offers considerable advantages. Patients with rare diseases benefit in particular.

A central component of the National Strategy genomDE is the model project on genome sequencing pursuant to Section 64e of the German Social Code, Book V (SGB V). The project comprises quality-assured, standardised diagnostics and therapy identification based on genome sequencing, delivered in accordance with the current state of science and technology, for rare and oncological diseases. The model project was successfully launched in July 2024. Key foundations include:

Anationwide uniform contract between the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and healthcare providers, concluded in July 2024 and joined by private health insurance (PKV) in September 2024, ensuring uniform reimbursement of diagnostics and therapy identification based on tiered flat-rate payments;

- A nationwide, decentralised data infrastructure with the Federal Institute for Drugs and Medical Devices (BfArM) acting as platform operator and the Robert Koch Institute (RKI) serving as central trusted body to safeguard sensitive genomic and clinical patient data;
- Standardised, high-quality genomic and clinical data collection (based on the Genomic Data Ordinance) for use in healthcare delivery and, subject to consent, for research purposes, for example in the context of evaluating new pharmaceutical therapies.

The project could only be launched through close and consistent collaboration among all stakeholders involved[4] and continues to benefit from this shared commitment. With a minimum duration of five years, the model project aims to integrate genomic medicine into routine healthcare in Germany and pave the way towards regular care pro-

vision. It is subject to continuous independent evaluation.

During the project's duration, statutory health insurance (GKV) will invest up to € 700 million, thereby laying the groundwork for improved and innovative care for insured persons. This initiative is unprecedented worldwide, positioning Germany as a pioneer in this field[5]. As of December 2025, 30 university hospitals are participating in the model project. Based on a uniform core dataset[6], they systematically collect both clinical and genomic data from treated patients. Prior to participation, hospitals were assessed by the GKV-Spitzenverband to ensure they meet the necessary personnel and technical requirements to provide these complex services within a quality-assured framework.

By combining clinical and genomic data within a secure data infrastructure, the project enables knowledge-generating care that benefits both participating patients and future affected individuals. With appropriate consent, collected data may be made available for research upon application. The data are pseudonymised and provided within a secure processing environment.

This enables the identification of causal genetic alterations and molecular mechanisms, facilitates more targeted and accelerated pharmaceutical development, and improves diagnosis and prognosis regarding disease risks, therapeutic options and treatment courses. The model project thus also strengthens Germany's position as a pharmaceutical innovation hub.

From our perspective, the genome sequencing model project represents a milestone for patient care and for the further development of personalised medicine in Germany. Currently, a total of twenty-one ATMPs are authorised. It provides the most advanced and sophisticated method currently available for investigating the presence of rare genetic diseases and for formulating therapy recommendations. Young patients in paediatrics and their families particularly benefit from this approach.

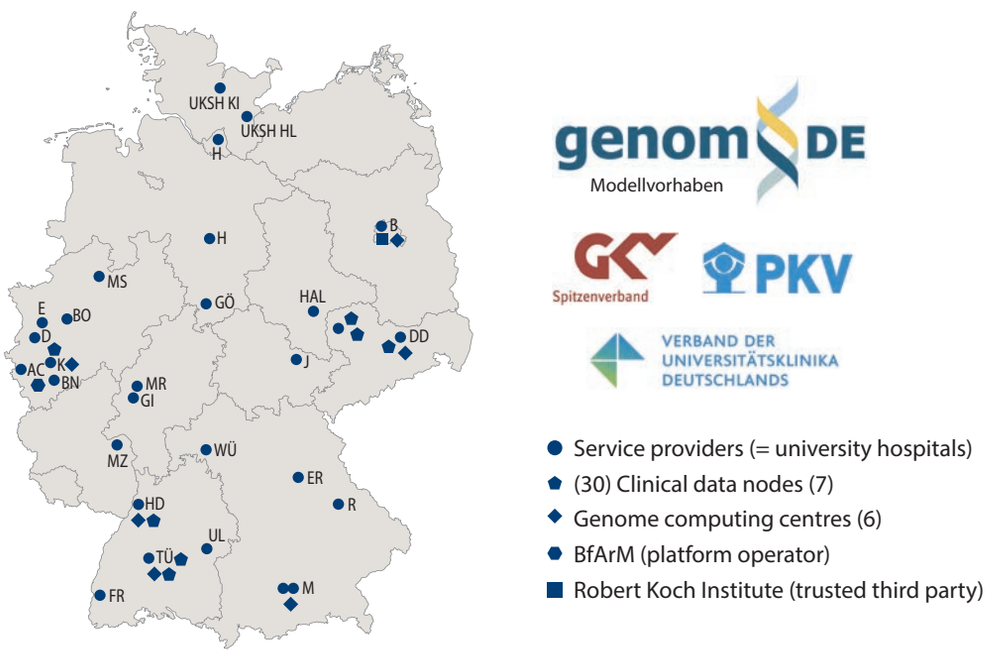
The Federal Ministry of Health and the platform operator are already working on future data linkage initiatives. A key priority is the linkage with data from the Health Research Data Centre. Another major objective is European integration of the model project within the framework of the European 1+ Million Genomes Initiative[7]and in alignment with the European Health Data Space Regulation.

The genome sequencing model project establishes an innovative research and care infrastructure that may serve as a blueprint for other innovative areas, in the spirit of a learning, evidence-based and sustainably financed healthcare system[8]. Building on the positive experience gained from the genome sequencing model project and following an initial exchange with experts, the Federal Ministry of Health (BMG) is currently developing a model project for ATMP Innovation Centres. The aim is to offer patients for whom no authorised therapies are currently available a treatment option using ATMPs, such as CAR T-cell therapies, within a structured, knowledge-generating and quality-assured care pathway as part of a model framework.

Biotechnological platforms such as CAR-T therapies and gene-editing technologies offer significant opportunities for patients but also impose the highest standards in terms of technological expertise within hospitals and quality assurance of manufacturing processes. The ATMP Innovation Centres model project is intended to ensure that specialised centres in Germany keep pace with developments and establish appropriate structures.

The development of innovative therapeutic approaches within the academic setting, combined with structured data collection, can make an important contribution to advancing innovative therapies and their further development, thereby helping to bridge translational gaps or avoid delays, for example in small patient populations. At the

Research and care infrastructure within the genomic sequencing pilot scheme



Source: genomDE platform operator, BfArM

Figure 2: The Genome Sequencing Model Project establishes an innovative research and healthcare structure that may serve as a model for other areas, in the spirit of a learning, evidence-based healthcare system.

same time, the model project addresses key objectives of the federal coalition agreement, in particular strengthening Germany as a pharmaceutical and biotechnology location, enabling access to and sustainable financing of innovative therapies, and contributing to the reduction of bureaucratic barriers.

In the further development of the ATMP Innovation Centres model project, the mandate under Section 4c of the German Medicines Act to develop a concept for an indication-specific ATMP registry will also be taken into account. The concept must be submitted by 31 December 2027; initial work has already commenced.

Selected EU initiatives in the field of biotechnology

With the EU Life Sciences Strategy published on 2 July 2025,[9] the European Commission aims to reposition the European Union as a global leader in life sciences innovation by 2030. Supported by more than € 10 billion annually from the current EU budget, the strategy provides for a coordinated approach across the entire life sciences value chain. Health policy measures include, for example, facilitating cross-border clinical trials and strengthening Euro-

pean clinical research infrastructures. This also encompasses the establishment of European ATMP Centres of Excellence. Market access for life sciences innovations is to be accelerated.[10] A particular focus is also placed on data use and the application of artificial intelligence (AI) to drive breakthrough innovation.

Furthermore, on 16 December 2025 the European Commission presented its proposal for a European Biotechnology Act for the health sector (so-called EU Biotech Act I).[11] The legislative proposal is of high priority for the Commission and forms part of broader political guidelines and several Commission initiatives and strategies (including biotechnology promotion and the Life Sciences Strategy). Through this proposal, the Commission aims to strengthen the health biotechnology sector within the EU. Key elements include project funding and improved patent protection through the extension of supplementary protection certificates, acceleration and simplification of clinical trial procedures (including with regard to ATMPs), as well as support for health innovation and measures relating to data use and artificial intelligence.

Given the growing importance of biotechnology for pharmaceutical care and its increasing economic and strategic relevance, we welcome the European Commission's initiative. It is essential to move forward swiftly to ensure, on the one hand, that patients gain rapid access to scientific advances and innovations and can benefit from them, and, on the other hand, that the EU's global competitiveness is strengthened.

Perspectives on costs, reimbursement and HTA

Pharmaceutical expenditure

For the first to third quarters of 2025, official statistics show an increase in pharmaceutical expenditure of six per cent (+ € 2.5 billion). This rate of increase is below the growth in total statutory health insurance (SHI) expenditure over the same period, which amounted to approximately 7.8 per cent, but remains above the average for the years 2013 to 2024 (5.6 per cent) and significantly above the long-term growth in revenues.

In 2025, expenditure dynamics in the pharmaceutical sector remain below those of the two other major spending categories: hospital treatment, which increased by 9.9 per cent (+ € 7.4 billion), and outpatient medical care, which rose by 7.6 per cent (+ € 2.9 billion). Contribution revenues increased by 5.3 per cent over the same period. In 2024, pharmaceutical expenditure had risen by 10.7 per cent (+ € 5.4 billion), particularly due to the expiry at the end of 2023 of the temporary increase in the manufacturer rebate.

The rise in pharmaceutical expenditure is driven, on the one hand, by cost and pricing dynamics associated with highly innovative patent-protected pharmaceuticals. Patent-protected pharmaceuticals account for more than 50 per cent of total pharmaceutical expenditure, while representing fewer than 10 per cent of prescriptions. This indicates that prescriptions of expensive innovative active substances are strongly focused on specific patient groups, for example in oncology. For the years 2026-2027, continued dynamic growth in pharmaceutical expenditure is forecast, partly due to new developments such as personalised therapies. According to recent data from the Scientific Institute of the AOK,[12] the rate of change in net costs for these pharmaceuticals was 6.9 per cent, indicating that the non-patent pharmaceutical segment also gained momentum in 2024.

The federal coalition agreement provides for stabilising the financial situation of statutory health insurance in order to avoid further increases in contribution rates, through a comprehensive package of structural adjust-

ments and short-term measures, while maintaining a high quality and level of services. Proposals are to be developed by an expert commission involving the social partners.

At the same time, the coalition agreement sets out the objective of making Germany the world's most innovative location for chemicals, pharmaceuticals and biotechnology. The framework conditions for the development and production of pharmaceuticals, active substances and medical devices are to be further improved. The industrial health sector, in particular the pharmaceutical industry and medical technology sector, is to be strengthened as a leading industry. It is envisaged that AMNOG will be further developed with regard to its regulatory „guardrails" and with a focus on personalised medicine.

Pricing & pay-for-performance

Gene and cell therapies administered as one-off treatments and associated in some cases with very high upfront costs have been available in German healthcare for several years. They are made available to eligible patients immediately following market launch and have successfully undergone the AMNOG procedure.

At present, the financial burden on statutory health insurance (SHI) resulting from these therapies remains limited despite their very high one-off prices, due to the very small patient populations and currently low market penetration. In the longer term, however, gene and cell therapies may also become relevant for the treatment of more prevalent conditions, for example neurological diseases such as Parkinson's disease.

These pharmaceutical therapies therefore illustrate the structural tension between the legitimate interest in ensuring the earliest possible availability of new treatments and the need to safeguard the financial stability of SHI. Gene and cell therapies must therefore not only continue to be developed for new medical indications; further development must also address the efficiency of production processes. Manufacturing processes need to become faster, simpler and more automated in order to make gene therapies accessible to broader patient populations.

Very high prices for gene therapies put the solidarity-based financing of statutory health insurance to the test. In this context, the option of pay-for-performance (P4P) models is being discussed among stakeholders. Pay-for-performance agreements are outcome-based reimbursement models in which the costs of a pharmaceutical therapy are linked to the respective treatment outcome. Given the high upfront costs and the uncertainty regarding long-term effects, such models are increasingly being considered in connection with gene therapies. The agreements already reached between the National Association of Statutory Health Insurance Funds (GKV-SV) and individual companies on P4P reimbursement amounts (e.g. Zynteglo®, Roctavian® or Hemgenix®) reflect this development.

However, depending on their specific design, pay-for-performance agreements may entail high transaction costs. This is particularly the case because individual patient outcomes must be observed, measured and evaluated over extended periods in order to assess the defined performance parameters. It is for the respective contracting parties to decide whether, and in what form, outcome-based remuneration models are agreed in individual cases, either within collective agreements or on a selective contractual basis. This issue will also form part of the ongoing pharmaceutical dialogue.

EU-HTA

At EU level, the first Joint Clinical Assessments (JCAs) of new pharmaceuticals are currently being conducted. In line with the phased implementation of Regulation (EU)

2021/2282 (EU HTA Regulation), the process initially covers oncological pharmaceuticals and ATMPs. At present, twelve products are undergoing assessment at EU level. The first assessment conclusions are expected in approximately the second quarter of 2026.

Pharmaceuticals subject to joint clinical assessment at EU level will continue to undergo national benefit assessment pursuant to Section 35a of the German Social Code, Book V (SGB V) upon market entry in Germany. In this context, the requirements of the EU HTA Regulation must be observed within the national HTA procedures. To this end, the German Ordinance on the Benefit Assessment of Pharmaceuticals (Arzneimittel-Nutzenbewertungsverordnung) was amended with effect from 8 March 2025.[13] The initially limited amendments are intended to ensure appropriate alignment between the European and national procedures. In particular, the pharmaceutical company decides to what extent the evidence submitted at EU level, which, due to the European prohibition of duplicate submission requirements, does not need to be re-submitted, is to be used for the national benefit assessment and refers to the relevant documentation accordingly (cross-reference approach).

The Federal Ministry of Health (BMG) is closely monitoring the introductory phase of the joint clinical assessments at EU level, will evaluate the outcomes and, where necessary, introduce further adjustments to the national benefit assessment procedure, in particular with the aim of avoiding duplication of work.

Outlook

The current global environment and its developments present new challenges for the pharmaceutical industry. In particular, US pharmaceutical policy, including tariff arrangements and the Most-Favoured-Nation concept, poses significant challenges for the sector.

Despite the political agreement in principle reached between the EU and the United States in July 2025 concerning tariffs, including on pharmaceuticals, further discussions in this area cannot be ruled out. In addition, the US administration is concluding agreements with pharmaceutical companies under the so-called Most-Favoured-Nation concept, with the aim of achieving price reductions in the United States at the level of comparable developed countries, while at the same time exerting pressure for price increases in those countries.

This makes it all the more important to further strengthen the pharmaceutical industry as a leading sector in Germany, as set out in the coalition agreement. The pharmaceutical industry is a key pillar of Germany as a business and industrial location. Beyond its contribution to growth and employment, the industry's innovative capacity directly benefits patient care.

For this reason, the Federal Government, under the leadership of the Federal Ministry of Health (BMG), is conducting the Pharmaceutical and Medical Technology Dialogue. The objective of this dialogue, and of the strategy to be developed on this basis, is to provide clear impetus for research, development and production, to strengthen the competitiveness of the sector, and to position Germany as a global innovation and production hub. The dialogue seeks to identify current challenges and future developments in order to develop sustainable solutions jointly. All ministries with relevant responsibilities are involved in the process to ensure coordinated framework conditions across policy areas that promote innovation and investment.

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ATMP and rare diseases: Regulatory initiatives and perspectives

Professor Dr Daniel Nowak, Professor Dr Stefan Vieths | Paul-Ehrlich-Institute (PEI)

Advanced Therapy Medicinal Products (ATMPs) constitute a growing and innovative class of pharmaceuticals, including gene therapies, somatic cell therapies, and tissue-engineered products. They open up new therapeutic options, particularly for patients with rare or serious diseases. As the clinical development and approval of these products progresses, the importance of adapted regulatory frameworks and efficient assessment procedures is increasing. National and European authorities face the challenge of enabling scientific innovation while upholding high standards for quality, safety, and efficacy. This article provides an overview of the legal basis, regulatory consultation and authorisation practices, the implementation of the Medical Research Act (MFG), as well as current measures to harmonise and ensure quality in the field of ATMPs.

The role of ATMPs in European Medicines Law

ATMPs have been governed at the EU level by Regulation (EC) No. 1394/2007 since 2008.[1] They represent a highly dynamic product category that often marks a shift from conventional to personalised therapies. In the past decade, more than 20 ATMPs have been authorised in Europe, with a predominance of CAR-T cell therapies in haematological oncology and gene therapies for rare genetic disorders such as spinal muscular atrophy, retinal dystrophies, and haemophilia A/B.[2]

Marketing authorisation applications for ATMPs are coordinated at the European level by the European Medicines Agency (EMA) and evaluated by the Member States through the Committee for Advanced Therapies (CAT), the Committee for Medicinal Products for Human Use (CHMP), and the Pharmacovigilance Risk Assessment Committee (PRAC). A complete authorisation procedure typically takes 12 to 15 months. The Paul-Ehrlich-Institute (PEI) acts as the national competent authority for the assessment, consultation, and monitoring of ATMPs and is also actively involved in European expert committees.

Within the centralised EU authorisation procedures, the PEI has taken on the role of Rapporteur (Rapp) or Co-Rapporteur (Co-Rapp) in 10 of the 21 ATMPs authorised to date and has participated as a Concerned Member State (CMS) in 11 further procedures. This high rate of Rapporteur or Co-Rapporteur involvement of nearly 50% highlights the Institute's pivotal role in Europe and its scientific and regulatory expertise in the field of advanced therapies.

Scientific advice and regulatory support

One of the PEI's core activities is providing scientific advice to companies, academic developers, and clinical institutions. These consultations aim to clarify study design, quali-

ty requirements, and regulatory issues early in development, thus helping to reduce risks and facilitate clinical trial applications or marketing authorisation procedures. Demand for consultations at the PEI and its department responsible for ATMPs, Haematology, Cell and Gene Therapy (HZG), remains consistently high, and the Institute aims to further expand its offerings.

In 2024, the HZG department conducted a total of 73 consultations, supplemented by written queries and external expert support. In the first half of 2025 alone, 53 consultations had already taken place. At the same time, waiting times were significantly reduced through targeted prioritisation, process control, and closer coordination among internal expert groups. Despite unchanged staffing levels, the consultation output increased, evidence of the effectiveness of organisational adaptations and the high relevance of scientific advice for the clinical development of ATMPs in Germany.

Implementation of the Medical Research Act (MFG)

The Medical Research Act (MFG), which came into force in 2024, aims to accelerate approval processes for clinical trials and optimise collaboration between the federal regulatory agencies.[3] For ATMPs, this entails in particular:

- Shortened processing times at federal agencies for clinical trials,
- Central coordination of assessment procedures via the BfArM, and

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- The establishment of a specialised ethics committee for specific procedures (SEKbV) under Section 41c of the German Medicinal Products Act (AMG). Since 1 July 2025, the SEKbV has been responsible for certain clinical trials, including those involving new medicinal products in humans and ATMPs.[4]

These structural changes aim to strengthen Germany's position as a hub for biomedical research and enhance its competitiveness in the European context.

Harmonisation and quality assurance

The PEI is actively involved in the further development and interpretation of regulatory frameworks. In the area of Good Manufacturing Practice (GMP), newly introduced provisions under Sections 14(6) and 14(7) of the AMG now allow for the publication of official recommendations on the interpretation of GMP principles for ATMPs. The aim is to enable a practical and uniform national interpretation that provides greater planning security for manufacturers and inspectors alike. In addition, the PEI promotes dialogue between regulatory authorities, research institutions, and manufacturers to ensure consistent assessment of benefit-risk profiles.

Challenges and outlook

Despite significant progress in the development and regulation of ATMPs, key challenges remain in assessing their safety and efficacy. In particular, rare diseases often pose a tension between high unmet medical need, differing views on product innovation, and frequently limited clinical data. Small patient populations, heterogeneous disease courses, and individualised treatment approaches can complicate robust benefit-risk analyses.

This tension is unavoidable, but also productive. Dialogue between applicants and authorities helps close data gaps, improve study quality, and ultimately increase patient safety. Open and structured communication, particularly in the context of early scientific advice, has proven to be a valuable element in successful authorisation processes. Against this background, the Paul-Ehrlich-Institute assigns high priority to systematic evidence generation within clinical trials. Only under controlled conditions can data on safety, efficacy, and dosing be collected in a manner that is scientifically valid and reproducible.

By contrast, insights from post-authorisation follow-up or registry data tend to be less structured, inconsistently documented, and methodologically difficult to compare. While such data can provide valuable supplementary information, they cannot replace a systematically planned and conducted clinical trial. A robust benefit-risk assessment therefore requires study designs that enable targeted data collection and minimise bias. As Germany's scientific and regulatory lead authority, the PEI supports the continued development of evidence-based assessment approaches and works to strengthen the methodological foundations for reliable benefit–risk assessments of ATMPs.

Conclusion

With its scientific and regulatory expertise, the Paul-Ehrlich-Institute makes a key contribution to the successful development and safe application of ATMPs in Germany and Europe. Through increased efficiency in consultation services, new tools for harmonisation, and close collaboration with European partners, the Institute reinforces the translational bridge between research, authorisation, and health technology assessment. The measures presented here demonstrate that regulatory innovation and scientific excellence must go hand in hand to sustainably improve care for patients with rare diseases.

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ATMP and orphan drugs in the AMNOG procedure

Dr Rimma Berenstein | Deputy Head of the Pharmaceuticals Department, Federal Joint Committee (G-BA)

For advanced therapy medicinal products (ATMPs) and orphan drugs, the comparative evidence available at the time of the benefit assessment pursuant to Section 35a of the German Social Code, Book V (SGB V), is frequently limited. This is often attributable to the complexity of the therapeutic approaches and the small patient populations for whom these products are developed. As a result, the planning and conduct of randomised controlled trials are associated with considerable challenges.

Definition of Advanced Therapy Medicinal Products (ATMPs) and orphan drugs

- Gene therapies, in which the therapeutic, prophylactic or diagnostic effect is based on the introduction of recombinant genes into the body.
- Somatic cell therapies, characterised by manipulated cells or tissues whose biological characteristics have been altered, or by cells or tissues that are not intended to be used for the same essential functions in the body.
- Tissue-engineered products, which contain modified cells or tissues intended for the repair, regeneration or replacement of human tissue.

To date, following recommendations by the European Medicines Agency (EMA), approvals have predominantly been granted for gene therapies in the fields of haematology and haemato-oncology. After market entry in Germany, these products have subsequently been assessed within the framework of benefit assessment (e.g. CAR T-cell therapies for the treatment of lymphomas, as well as other gene therapies for the treatment of haemophilia, sickle cell disease and β-thalassaemia). More recent approvals of gene therapies also concern further indications with previously limited treatment options, such as epidermolysis bullosa (DEB).[2]

The authorisation of ATMPs is frequently associated with the granting of orphan drug status. Orphan drugs are products intended for the treatment, prevention or diagnosis of a life-threatening or chronically debilitating disease, provided that the prevalence of the condition in the European Union (EU) does not exceed 5 in 10,000. Moreover, either no satisfactory method of diagnosis, prevention or treatment must be authorised for the indication in question, or – if such a method exists – the pharmaceutical must provide a significant benefit for affected patients compared with existing treatment options.[3]

In determining the presence of a significant benefit compared with existing treatment options, criteria are applied that go beyond those specified in the Ordinance on the Benefit Assessment of Medicinal Products (AM-NutzenV) for the determination of additional benefit within the benefit assessment. Thus, in addition to improved efficacy and tolerability, the EMA also considers a meaningful contribution to patient care, for example in the form of facilitated self-administration or improved treatment adherence. Furthermore, the demonstration of improved efficacy and tolerability does not necessarily require a quantitative element but may also be based on qualitative assessment drawing on clinical experience.[4,5]

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Status quo of regulations for ATMP and orphan drugs in benefit assessment

As both ATMPs and orphan drugs are centrally authorised by the European Commission, these products are generally subject to benefit assessment pursuant to Section 35a of the German Social Code, Book V (SGB V). For gene therapies and somatic cell therapies, Section 35a(1b) SGB V requires the submission of evidence for the benefit assessment. For tissue-engineered products, it must still be examined whether they fall within the scope of the assessment of diagnostic and treatment methods pursuant to Sections 135, 137c or 137h SGB V. In most cases, however, tissue-engineered products are likewise assigned to the regulatory framework of Section 35a SGB V.

With regard to assessment standards, no specific provisions apply to the ATMP product class within the benefit assessment. Accordingly, ATMPs are also required to provide evidence of additional benefit in relation to an appropriate comparator therapy.

If an ATMP simultaneously holds orphan drug status, the special provisions defined in Section 35a(1), sentence 11, SGB V apply. Under these provisions, the additional medical benefit is deemed proven by virtue of marketing authorisation, and evidence in comparison with an appropriate comparator therapy does not need to be submitted. If the turnover of an orphan drug reimbursed by the statutory health insurance exceeds EUR 30 million within a twelve-month period, this privilege ceases to apply, and the pharmaceutical company is required to submit evidence of additional medical benefit in comparison with an appropriate comparator therapy as part of a renewed benefit assessment.

As orphan drugs may receive indication-specific market exclusivity, the Federal Joint Committee (G-BA) conducts benefit assessments only in those indications of orphan

drugs for which active protection rights in the form of data exclusivity and/or market exclusivity still exist.[6]

Since 12 January 2025, Regulation (EU) 2021/2282 on health technology assessment at EU level has been in force. The first products to be assessed are oncological products and ATMPs, including those holding orphan drug status. From January 2028 onwards, the assessment framework will be extended to all other orphan drugs.[7]

The G-BA participates as a member of the HTA Coordination Group and its associated subgroups in the preparation of Joint Clinical Assessments (JCA). The procedure begins with validation of the marketing authorisation application by the European Medicines Agency (EMA). Subsequently, the assessment scope (PICO framework) for the respective pharmaceutical is agreed between the Member States and communicated to the pharmaceutical company for dossier preparation. In this process, the G-BA provides feedback on the assessment scope considered relevant from a German perspective. As no exemptions apply for orphan drugs at EU level, a comparator that represents an appropriate benchmark taking into account the national healthcare context is likewise defined and notified by the G-BA in these cases.

Outcomes of benefit assessments for orphan drugs and ATMPs

Orphan drugs and, in most cases, ATMPs are developed for indications with comparatively small patient populations. Accordingly, benefit assessment decisions predominantly report a number of patients covered by statutory health insurance of fewer than 1,000 patients, and in approximately one third of cases even fewer than 100 patients. At the same time, ATMPs in particular represent complex therapeutic approaches, often based on the genetic manipulation of patient-specific cells.

This gives rise to considerable challenges in the design of randomised controlled trials (RCTs), for example with regard to the feasibility of blinding or the establishment of appropriate data collection structures for capturing patient-reported outcomes. Where these products are developed for treatment settings in which no causal therapeutic alternatives exist, ethical considerations may additionally render the recruitment of patients into a comparator arm consisting exclusively of best supportive care difficult.

As a result, marketing authorisation for these pharmaceuticals is often based solely on single-arm studies, making indirect or historical comparisons necessary for comparative benefit assessment. The submission of such non-randomised comparisons is, in principle, permissible within the benefit assessment framework and is therefore assessed by IQWiG and the G-BA. However, experience shows that in most cases no sufficiently robust conclusions for the benefit assessment can be drawn from the submitted non-randomised comparisons, owing to the use of unsuitable data sources or non-valid methodology.

Difficulties arise in particular where the compared patient populations differ substantially in their baseline characteristics, where data from the registry used are not suitable to address the benefit assessment question, or where the methodology presented in the dossier is inadequate or not transparent.

Indication-specific registries represent an important data source for the conduct of non-randomised or historical comparisons. However, existing registries have frequently been established without consideration of the requirements necessary to address benefit assessment questions. In many cases, there is no systematic identification of potential confounders within the indication, resulting in incomplete capture of relevant baseline characteristics within the defined dataset. In addition, data may be reported

irregularly, endpoint definitions may not be aligned with those used in clinical trials, or a high proportion of missing values may be present in the dataset.

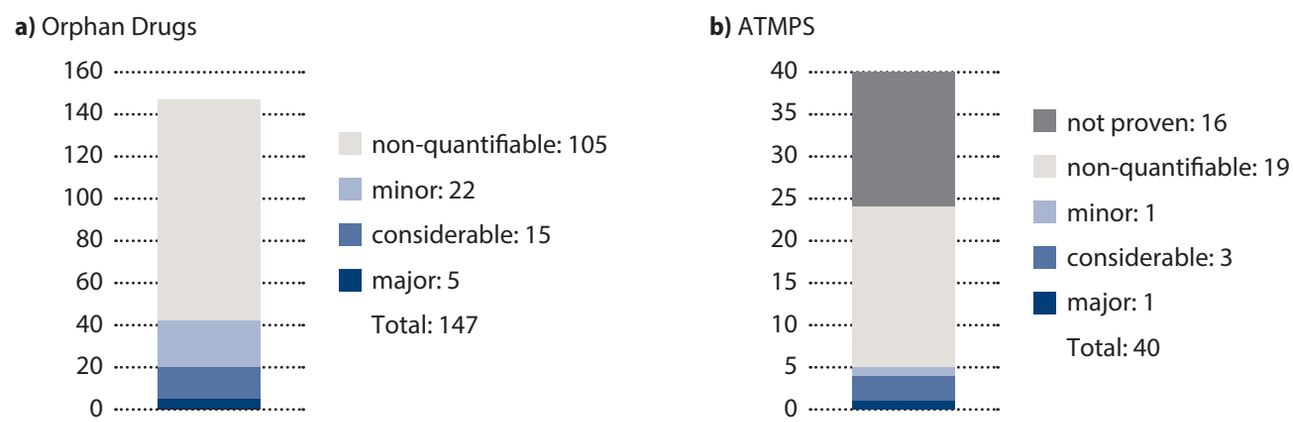
Further challenges arise from ongoing developments in the generally accepted state of medical knowledge, for example with regard to new tumour markers and prognostic factors that have not yet been captured in routine care. This can further limit the usability of retrospective data from indication-specific registries. Moreover, for many rare diseases, the necessary data collection within medical registries is fundamentally lacking, precluding the provision of suitable data for benefit assessment.

Overall, no assessable data for benefit assessment are available for at least 50 per cent of orphan drug and ATMP procedures (figure 1). In addition, data on health-related quality of life are often not collected at all in single-arm studies (figure 2). As benefit assessment is inherently a comparative exercise, quantification of additional benefit is generally not possible on the basis of single-arm study data or methodologically inadequate non-randomised comparisons. In situations where the conduct of an RCT is genuinely not feasible for ethical reasons, registry data from indication-specific medical registries may nevertheless allow for a non-randomised comparison, despite the challenges outlined above.

A prerequisite for this is that the data are suitable for addressing the benefit assessment question, are collected at a sufficiently high level of data quality, and are analysed using appropriate statistical methodology for non-randomised comparisons. This requires early and pre-specified planning by the pharmaceutical company, including the development of a study protocol and a statistical analysis plan.

In addition, the selection of the data source must ensure

Results of benefit assessments for orphan drugs and ATMPs (status of valid resolutions as of December 2025)



Source: G-BA

Figure 1: For at least 50 per cent of benefit assessments of orphan drugs and ATMPs, no assessable data are available.

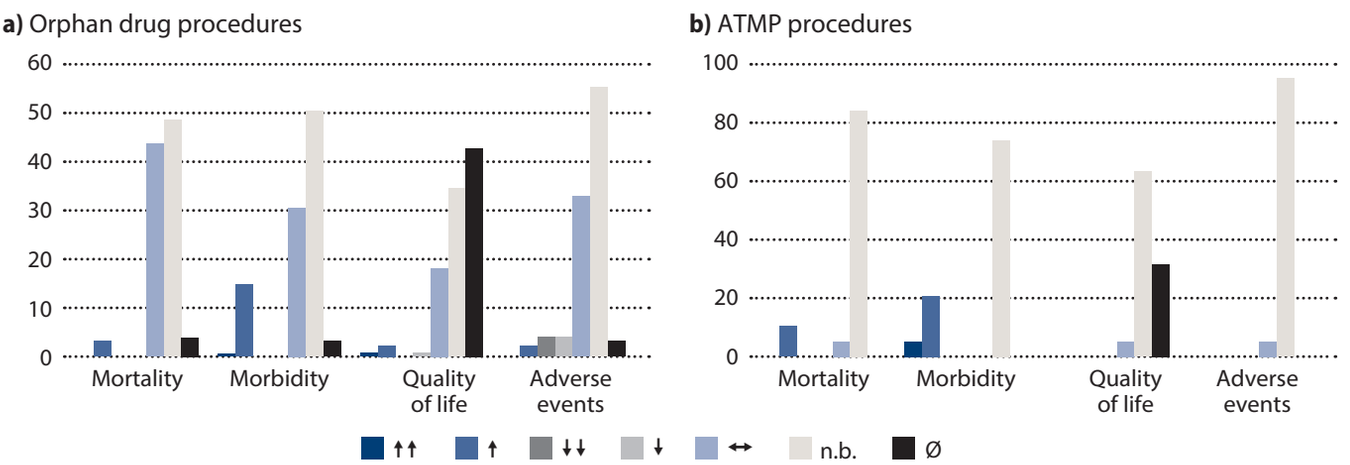
that all relevant parameters that can be collected within routine care are documented for the indication under consideration. Where this is not the case, corresponding data fields should be added to the data source As prospective generation of routine care comparator data or data on the natural course of disease following market entry of a new medicinal product can be particularly challenging in treatment settings without causal therapeutic options, data collection within a registry should ideally be initiated in parallel with the conduct of the clinical trial or prior to market entry of the pharmaceutical.

Furthermore, the submission of data from alternative study designs (e.g. platform trials) is also, in principle, permissible for benefit assessment where these allow for a comparative evaluation of treatment effects. However, to improve both the use and the interpretability of data from medical registries or alternative study designs for benefit assessment, targeted investment is required to support the establishment of suitable registry structures and to further develop the research data infrastructure in Germany.

It must be distinguished from the ethical considerations outlined above that pharmaceutical companies may decide, for economic or other strategic reasons, not to conduct a comparative clinical trial. An increasing proportion of orphan drugs are being developed in indications for which causal therapeutic approaches already exist. An evaluation by the EMA of the orphan drug regulation showed that only 28 per cent of orphan drugs were not required to demonstrate a significant benefit compared with existing treatment options.[8]

Moreover, more than 50 per cent of orphan drugs are developed for indications with a prevalence exceeding 1 in 10,000, whereas 96 per cent of rare diseases have a prevalence below 1 in 10,000.[9] The argument of a lack of treat-

Summary of results for relevant clinical endpoints (status: September 2025)



Source: G-BA

Figure 2: The results of the assessment of relevant clinical endpoints indicate that, for orphan drugs and ATMPs, data on health-related quality of life are frequently not collected.

ment alternatives preventing a comparative study design on ethical grounds, or of insufficient patient numbers to allow adequate recruitment, therefore does not apply to the majority of orphan drugs currently under development.

In addition, numerous examples from procedures conducted under Section 35a SGB V demonstrate that valid RCTs can be conducted even in indications with very small patient populations (e.g. fewer than 100 patients) and can be used for benefit assessment.[10,11,12] Even complex therapeutic approaches such as CAR T-cell therapy do not, per se, preclude the conduct of comparative clinical trials, as evidenced by several benefit assessment procedures in early lines of therapy for diffuse large B-cell lymphoma (DLBCL) and multiple myeloma.[13,14,15,16]

It is undisputed, however, that for ultra-orphan indications with a prevalence of less than 1 in 50,000, situations may arise in which RCTs are not feasible due to the extremely small patient populations.

Role of routine practice collection

Pursuant to Section 35a(3b) of the German Social Code, Book V (SGB V), the Federal Joint Committee (G-BA) has the authority to require the collection and evaluation of routine practice data from the pharmaceutical company. This authority is limited to pharmaceuticals with orphan drug status or to pharmaceuticals that have received conditional marketing authorisation or authorisation under exceptional circumstances.

The G-BA may restrict the authorisation to provide care with a pharmaceutical for which such data collection has been required to those healthcare providers who participate in the data collection. In addition, the G-BA must define requirements regarding the duration, type and scope of data collection and evaluation, including specifications on methodology as well as on patient-relevant endpoints and their assessment.

At present, five routine practice studies are ongoing, four of which concern ATMPs (onasemnogene abeparvovec [spinal muscular atrophy], brexucabtagene autoleucel [mantle cell lymphoma], etranacogene dezaparvovec [haemophilia B], and valoctocogene roxaparvovec [haemophilia A]). The first benefit assessment based on routine practice data collection is expected to be conducted in mid-2027 for onasemnogene abeparvovec, seven years after the pharmaceutical entered the market.

Given the existing challenges in registry structures in Germany, routine practice data collection does not represent a suitable instrument for closing evidence gaps for orphan drugs and ATMPs in a timely manner within the benefit assessment. In particular, a decision to require routine practice data collection can only take effect once the pharmaceutical has entered the market, after which a time-consuming coordination process with the pharmaceutical company regarding the study documentation follows.

Although comprehensive modifications to the data source are often necessary in order to address the benefit assessment question, the G-BA cannot impose direct requirements on registry operators themselves, but only on the respective pharmaceutical company. This substantially delays the initiation of data collection. Due to the additional study duration required to ensure an adequate observation period for endpoints, relevant data for benefit assessment are therefore often not available until several years after market entry.

Furthermore, owing to the non-randomised nature of routine practice data collection, a sufficiently large patient population is required to allow appropriate adjustment for potential effect modifiers (confounders). For feasibility, this necessitates at least 100 patients within the indication.

Consequently, routine practice data collection does not allow for a meaningful closing of evidence gaps even in the case of ultra-orphan indications.[17]

Conclusion and outlook

Orphan drug status or classification as an ATMP should not be equated with a lack of feasibility of conducting a randomised controlled trial (RCT). In specific treatment settings, for example where causal therapeutic approaches are lacking or in the context of very rare diseases, the conduct of an RCT may be associated with particular challenges and, in individual cases, may indeed not be possible for ethical reasons. However, this must be distinguished from therapeutic situations in which an RCT would in principle be feasible, but the pharmaceutical company decides against conducting such a study for strategic or economic reasons due to the associated challenges. As a result, quantification of additional benefit within the benefit assessment is generally not possible when based on single-arm study data.

A proactive expansion of the research data infrastructure in Germany, including indication-specific registry structures, can be used to strengthen the evidence base for orphan drugs and ATMPs and to make this evidence accessible for benefit assessment. For the efficient and timely closing of evidence gaps, data structures must be established at an early stage in order to collect comparative data even before market entry of a pharmaceutical and to create opportunities for the implementation of new study designs. This approach can also enable methodologically appropriate non-randomised comparisons with data on the natural course of disease or historical cohorts, including in indications for which no suitable treatment options have previously been available.

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ATMP and rare diseases: Potential and challenges

Dr Henning Kleine | Director Market Access and member of the Executive Management at AbbVie Deutschland GmbH & Co. KG

An increasing number of rare diseases can now be treated with targeted therapies, and pathophysiological processes previously considered untreatable are becoming therapeutically accessible. Gene and cell therapies play a significant role in this progress, as they offer new molecular targets and can result in improved benefit–risk profiles. However, these innovative treatment approaches regularly pose challenges for benefit assessment and reimbursement: therapies for small patient populations or for one-time administration are frequently approved through study designs that satisfy regulatory requirements for assessing efficacy and safety, yet make it difficult to demonstrate an additional benefit due to high methodological barriers. At the same time, new reimbursement models must be developed, especially when therapy costs that would typically accrue over years for chronic treatments are concentrated into a single administration.

New opportunities through ATMPs and orphan drugs

Advanced Therapy Medicinal Products (ATMPs) include gene therapies, somatic cell therapies, and tissue-engineered products.[1] These therapies are often aimed at patients with high unmet medical need and no satisfactory treatment options. This is reflected in the high proportion of ATMPs among the pharmaceuticals classified as „Priority Medicines" (PRIME) by the EMA: as of August 2025, more than one third of 96 PRIME-designated pharmaceuticals were ATMPs.[2]

An analysis of the ATMPs assessed by the EMA (as of 2024: 27 products) likewise underlines the significant medical need targeted by this class of pharmaceuticals: 52% had received PRIME status, and 74% had orphan drug designation.[3]

While CAR-T-based ATMPs are most often associated with oncology, a review of PRIME-designated ATMPs reveals development across a broad range of therapeutic areas. Of the 36 products analysed, 12 were in oncology, 8 in endocrinology (including some hereditary forms), 6 in congenital disorders, 5 in ophthalmology, 2 in immunology, and 3 in other fields.[4]

ATMPs frequently offer ways to intervene in pathophysiological processes for which small molecules or biologics have no therapeutic leverage. One example of experimental ATMP use outside of oncology is anti-CD19 CAR-T therapy for refractory systemic lupus erythematosus (SLE). SLE is associated with a more than five-fold increased mortality risk in incident patients under the age of 45.[5]

Treatment with anti-CD19 CAR-T in five patients under the age of 25 with therapy-refractory SLE and multi-organ involvement resulted in durable, therapy-free clinical remission in all five cases.[6] Building on this highly relevant proof-of-concept, multiple CAR-T candidates are now in

clinical development for autoimmune diseases. Still, ATMPs remain a niche product in the overall market for prescription pharmaceuticals: in 2024, 43 new innovative pharmaceuticals were launched in Germany, none of which were gene or cell therapies.[7]

Market access challenges for ATMPs and orphan drugs

ATMPs and orphan drugs represent essential – and sometimes the only – treatment options for many patients. However, differing national regulations across EU member states and methodological hurdles in benefit assessment impact patient access to these therapies.

Inconsistent assessments within the EU

A key challenge in the use of already authorised ATMPs lies in their routine integration into healthcare delivery. An analysis of 18 ATMPs approved by the EMA up to the end of 2023 revealed significant disparities in availability across 23 of the 27 EU countries studied. ATMP availability was highest in Germany (89%), followed by France and Italy at 61% each. Only one third of the ATMPs analysed were available in more than one third of the countries assessed. Three of these six were CAR-T therapies for haematological malignancies with multiple indications.[8]

In addition to issues such as the need for certified treatment centres, limited specialist care in rural areas, or the complex supply chains of CAR-T products, benefit assessment procedures warrant closer scrutiny. An analysis of HTA outcomes for ATMPs in Germany, France, Italy, and the Netherlands revealed considerable variability in the level of recognised additional benefit. In Italy, all five gene therapy indications assessed were granted a significant additional benefit and innovation status (i.e. highest category of added benefit). In contrast, only one out of eight evaluations in France was assigned a significant additional benefit (ASMR II), while six out of eight received a moderate rating. In Germany, the Federal Joint Committee (G-BA) assigned a non-quantifiable additional benefit in six of eight cases, reflecting the statutory minimum benefit conferred by orphan drug status.[9] One possible explanation for the relatively lower ratings in Germany compared to Italy may be the high evidence requirements, which often cannot be met in the context of highly specialised therapies.

Challenges due to small patient populations

ATMPs often target small patient populations: in 30 out of 38 procedures, the G-BA identified fewer than 1,000 eligible patients. As a result, ATMPs face similar challenges in the AMNOG process to those encountered more broadly by pharmaceuticals for rare diseases.[10]

Since the EU Regulation on Orphan Medicinal Products was introduced more than 25 years ago, development and

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ATMPs and orphans – Figures and facts

36 PRIME-ATMPs
approx. 1/3 of all priority medicines

27 ATMPs 2024 EMA
(<1/2 with PRIME and approx. 3/4 with orphan status

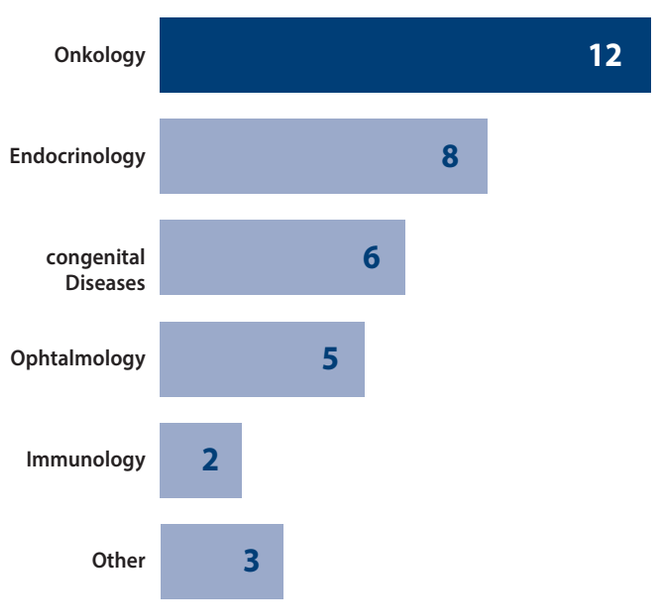
3,000+ orphan designations
approx. 1/3 of all priority medicines

260+ Orphan approvals

Source: EMA

Figure 1: The high medical need addressed by ATMPs is also reflected in the fact that 52% of the substances received PRIME designation.

Therapeutic areas of current PRIME-designated ATMPs



Source: [4]

Figure 2: The therapeutic areas of current PRIME-designated ATMPs are primarily oncology, endocrinology, congenital diseases, and ophthalmology.

approval of orphan drugs has significantly accelerated, with over 3,000 orphan designations granted and more than 260 products authorised.[11] This expansion of therapeutic options is a welcome development for affected patients and can rightly be regarded as a European success story. Occasionally, the increasing number of orphan drugs prompts allegations of deliberate „salami slicing" to secure OD status, i.e. the artificial narrowing of patient populations. However, such a practice is not permissible from a regulatory standpoint. [12,13]

On the contrary, in practice, pharmaceuticals with multiple indications often lose their OD status when a new indication within a broader non-orphan population is approved. This results in a dual submission obligation, requiring a full assessment for the existing indication and a new submission for the added one. Moreover, around 80% of orphan drug revenues in Germany are now subject to full benefit assessment, triggered by exceeding the € 30 million annual revenue threshold (vfa analysis, 2023).

While the development of ATMPs and orphan drugs is

more demanding due to the complexity of research in rare indications, it can be worthwhile when successful, thanks to substantial therapeutic innovation and often swift access to the market. Currently, orphan drugs account for approximately 20% of global prescription pharmaceutical sales. This proportion is expected to remain stable through the end of the decade, considering the number of orphan drugs in late-stage clinical development and projected global sales.[14]

Challenges of one-time therapies

In addition to small patient populations, many ATMPs face the challenge of proving the long-term, patient-relevant superiority of a one-time administration compared with ongoing therapy. Regulatory requirements can often be met through non-inferiority trials with shorter follow-up durations, but HTA requirements frequently call for additional randomised controlled trials with long-term, patient-relevant efficacy endpoints.

One example is RGX-314, an ophthalmology-focused ATMP. RGX-314 is a vector-based gene therapy delivered via intraocular injection, leading to sustained expression of a VEGF-inhibiting antibody. This approach may replace the currently widespread use of intravitreal anti-VEGF injections, potentially slowing visual deterioration in patients with wet age-related macular degeneration.[15]

The pivotal trials for RGX-314 consist of two Phase III studies (ATMOSPHERE and ASCENT), both designed as non-inferiority trials comparing RGX-314 to ranibizumab, with BCVA assessed at Week 52. An additional head-to-head (H2H) study, ACHIEVE, is ongoing. It compares a single administration of RGX-314 with as-needed ranibizumab treatment over five years, enrolling 187 patients per arm.

The complex H2H design aims to improve the probability of demonstrating an additional benefit. However, the markedly different treatment schedules between the gene therapy and the comparator pose challenges for study implementation and remain vulnerable to methodological critique, particularly regarding potential bias in the evaluated endpoints, even with rigorous study standards.

EMA statement on the conditions for granting orphan drug designation

> **The fact that a subset of patients exists in whom the medicinal product is expected to show al favourable benefit / risk (as defined in the proposed therapeutic indication) would generally not be sufficient to define a distinct condition.**

> **When evaluating an application for designation, the Committee on Orphan Medicinal Products will consider an orphan condition in broad terms in order to avoid designations related to artificial subsets of a particular condition.**

Source: [12, 13]

Figure 3: According to the EMA, it is not permissible from a regulatory perspective to artificially narrow patient populations through deliberate „salami slicing" in order to obtain orphan drug status.

A proposed solution: Recommendations from the National Strategy for Gene and Cell Therapies

There is no question that ATMPs and orphan drugs are of

high relevance for patients with serious illnesses. To ensure early and widespread access in Germany going forward, concrete recommendations have been outlined in the National Strategy for Gene and Cell Therapies.[16] Key elements include:

Recognition of best available evidence in benefit assessments: Legal frameworks and procedural regulations (AM-NutzenV, G-BA Rules of Procedure) should be revised. The focus should not be solely on the highest level of evidence, but on the best available evidence presented so that submitted studies must be considered.

Adjustment of criteria for using real-world data: Requirements for conditional data collection are disproportionately high. The appropriateness and feasibility of such measures should be evaluated early in the process, prior to formal request, with involvement from relevant stakeholders and the affected company.

Clarification of value-based pricing: The constraints introduced by the GKV Financial Stabilisation Act (GKV-FinStG) should be removed. The „non-quantifiable" category of additional benefit should revert to its original meaning (i.e. not less than „minor").

Greater use of outcome-based reimbursement models (pay-for-performance): While pay-for-performance contracts can already be established under §130b SGB V, structural changes to the morbidity-based risk adjustment (Morbi-RSA) are needed to incentivise new reimbursement models such as lump-sum or instalment payments. In addition, mechanisms for patient tracking, as recommended in the Federal Social Security Office's special report, must be implemented.

Standardisation and funding of diagnostics and quality assurance: Remuneration for complex and costly diagnostics, as well as coverage for quality assurance activities in treatment centres, should be ensured.

Standardised collection and documentation of real-world data: A national GCT (gene and cell therapy) registry should be established and digitally integrated to monitor treatment use, long-term safety, and effectiveness, and to facilitate evidence generation for non-approvable therapies. A non-profit operator structure is proposed, with funding from the state and, where appropriate, pharmaceutical companies.

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Data basis for ATMP and rare diseases from the perspective of patients

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Often Insufficient Data Basis

In procedures conducted by the Federal Joint Committee (G-BA) concerning advanced therapy medicinal products (ATMPs) and „classic" rare diseases, there is often a lack of sufficient data to quantify the additional benefit following marketing authorisation.

In many cases, only data from single-arm studies are available following approval. The reasons for this often lie in small patient populations associated with rare and severe progressive diseases, combined with a high unmet medical need.

If, for example, indirect comparisons are not feasible or dramatic effects cannot be derived from single-arm studies, the legislator has granted the Federal Joint Committee (G-BA) the option to request an routine practice data collection from the pharmaceutical company in order to enable a later quantification of the additional benefit.

To date, routine practice data collections have primarily been mandated in cases of serious, often life-threatening diseases with rapid disease progression, where the availability of the pharmaceutical promised a significant improvement in therapeutic options, e.g. n supportive or palliative settings. Typically, such cases also involved substantial methodological limitations in the study design or a lack of suitable long-term data on efficacy and safety. Additional prerequisites for initiating an routine practice data collection include the availability of existing registries and enough patients within the indication.

Ensuring availability of ATMPs for patients

Promising new pharmaceuticals should be made available to patients as quickly as possible, particularly in the case of severe and rare diseases. The requirements of routine practice data collections are also associated with restrictions to specific healthcare providers and renewed price negotiations, even if a routine practice data collection fails.

Potential conflicts of interest, such as the linkage between data generation and cost savings, appear to pose obstacles. Initial experience shows that implementing routine practice data collections is challenging. Criticism has been directed at the high methodological demands, such as the shifted null hypothesis and confounder adjustment, as well as the resulting long study durations.

Especially in dynamic therapeutic areas such as oncology, this may lead to a shift toward alternative treatment options that are not subject to routine practice data collection requirements, or to therapy switching that makes meaningful data evaluation impossible.

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Better data from the outset

Routine practice data collections often require very long periods before statistically significant differences in patient-relevant outcomes between intervention and control arms can be demonstrated. The requirements for routine practice data collections are that the data must show consistent results across outcome categories such as mortality, morbidity, severity of disease-specific symptoms, and adverse events using appropriate, established, and validated measurement instruments.

A particular challenge lies in the timing of patient-reported outcomes, especially those related to health-related quality of life. By the end of a study, the pharmaceuticals used in the control arm may no longer reflect the current standard of care. If the appropriate comparator therapy is not implemented, there is a risk that the Federal Joint Committee (G-BA) will not acknowledge an additional benefit.

Therefore, early and broad collection of patient data starting at the time of authorisation is of utmost importance and should be anticipated by pharmaceutical companies. This also raises key questions: What data do we need? What constitutes the best available evidence?

More effective data generation? Knowledge over hope

During the introduction of the AMNOG procedure in Germany, the concept of a „learning healthcare system" was frequently invoked. To improve the evidence base, new approaches must be considered and pursued, as previous experience with routine practice data collections shows that these procedures often take too long and are difficult to implement. Existing indication-specific registries should be expanded at national, European, and international levels. The exchange of data by pharmaceutical companies within registries should also not pose a barrier, especially when patient interests are at stake.

Nevertheless, recent decisions in early benefit assessments demonstrate that randomised controlled trials are both feasible and necessary, even in small patient populations. Valid indirect comparisons are also possible. This is particularly relevant in the context of gene therapies, especially in therapeutic areas such as haemophilia or sickle cell disease, where – despite the rarity of the conditions – effective and safe alternative therapies are already available, against which an ATMP should be compared. Patients must be able to weigh effectiveness against side effects.

It must be ensured that sufficient foundations are in place to enable the generation of adequate, high-quality, and meaningful data. Only then can a sound and knowledge-based assessment of the benefits and potential risks for patients take place, hope alone is not enough.

Data basis in rare diseases and ATMPs: What do we see? What would we like to see?

Dr Harald Herholz, MPH| Association of Statutory Health Insurance Physicians of Hesse

In recent years, the majority of Advanced Therapy Medicinal Products (ATMPs) and orphan drugs have been assigned a non-quantifiable additional benefit by the Federal Joint Committee (G-BA). Manufacturers often attribute this to factors such as insufficient patient numbers, short observation periods, or the impracticality of conducting RCTs or head-to-head trials. In 2019, a potential solution was introduced: Routine practice data collection. But the results have been disappointing. What alternatives do we have? One suggestion is to tie routine practice data collection directly to market authorisation. However, given the immediate reimbursement eligibility of pharmaceuticals in Germany, this would likely offer only minimal improvements. Another idea is to initiate data collection already in Phase II, before approval by the EMA. However, this approach also comes with technical challenges. For extremely small target populations of less than 100 patients real-world evidence strategies should be developed that enable comparisons either with the natural course of the disease or with the standard of care.

What do we see?

Over the past ten years, we have seen the same pattern repeatedly: the Federal Joint Committee (G-BA) assigns a non-quantifiable additional benefit to the majority of Advanced Therapy Medicinal Products (ATMPs) and orphan drugs. Unfortunately, there are only a few exceptions such as Luxturna® or Libmeldy®. Manufacturers often attribute this to the same factors such as insufficient patient numbers, short observation periods, or the impracticality of conducting randomised controlled trials or head-to-head trials.

In 2019, a potential solution was introduced: Routine practice data collection. The aim was to build a stronger data basis for a reassessment to establish a quantifiable additional benefit. One year later, in 2020, the first data collection process was launched with Zolgensma®.

But the results have been disappointing. Each case is subject to individual approval by the G-BA. Out of 69 potential candidates, only 20 application-related data collection procedures were initiated of which only nine were actually implemented. Two of these were terminated early. Five years on, only five active procedures are still collecting data. This hardly looks like a scalable solution.

The underestimated factor of time: when will results be available?

Another problem is the lengthy duration of the procedures which is up to 87 months in some cases, such as with Roctavian®. On average, the time between the initial G-BA decision and a reassessment is 6.5 years. This raises concerns that routine practice data collection, regrettably, does not deliver results that are suitable for a meaningful reassessment.

We also see that routine practice data collection proce-

dures or registries are not necessarily easier to conduct than randomised controlled trials for orphan drugs. The effort involved has been underestimated. Setting up a new registry alone takes 1.5 to 3 years on average, only then does data collection actually begin. As a result, the findings often come too late to support a reassessment before the patent expires. Long timelines also create formal issues, such as changes in the comparator (standard of care).

From the treating physicians' perspective, routine practice data collection can also have unintended negative effects. Prescription restrictions associated with the procedure can be burdensome. The required documentation effort can become significant, potentially deterring use and shifting preference toward alternative therapies that are not subject to such demands.

What alternatives do we have?

One suggestion is to tie routine practice data collection directly to market authorisation. However, given the immediate reimbursement eligibility of pharmaceuticals in Germany, this would likely offer only minimal improvements. The time gained would be minimal. It has therefore been proposed to start even earlier, in Phase II, that is, prior to EMA authorisation. However, this approach also encounters technical limitations and does not appear to be a sufficient solution on its own.

For pharmaceuticals with a target population exceeding 100 patients, conventional randomised controlled trials are likely to remain the most appropriate option. For extremely small target populations of less than 100 patients real-world evidence strategies should be developed that enable comparisons either with the natural course of the disease or with the standard of care, ideally conducted in parallel with authorisation studies.

Finally, I would like to address two questions raised by the patient representative during the platform conference: (a) What does this mean in practical terms for affected patients? (b) What do we as patients, doctors and health insurers actually need to know?

For patients, two questions are likely to be decisive: Is the benefit–risk ratio positive? This question can be answered through EMA authorisation.

Is the new pharmaceutical better than the current standard of care? This should be addressed through the G-BA's

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benefit assessment. But here lies the problem: a hypothetical, non-quantifiable additional benefit does not answer this clinically relevant question.

In principle, physicians in hospitals and private practices are interested in answering the same questions as patients. However, two additional questions arise from their perspective: First, is the pharmaceutical prescribable? This is determined by the G-BA's pharmaceutical directive. In general, most prescription-only pharmaceuticals are prescribable immediately after approval in Germany.

Second, when and by whom should the new pharmaceutical be used? The G-BA's benefit assessment currently provides guidance on this only in exceptional cases, under section 3 of its decisions titled „Requirements for quality-assured use". In particular, statutory health insurance physicians would welcome clearer guidance and more specific criteria here. The G-BA should make more frequent use of this regulatory scope.

AAV gene therapy in haemophilia: Clinical perspective on efficacy, safety, and integration into routine care

Professor Dr Wolfgang Miesbach | Department of Haemostasis and Haemophilia Centre, Medical Clinic 2, University Hospital Frankfurt

AAV-based gene therapy now represents a pioneering treatment option for adult patients with severe and, in some cases, moderately severe haemophilia. After more than 30 years of development, authorised gene therapies enable long-term endogenous factor expression and can sustainably improve patients' quality of life. At the same time, new challenges arise regarding regulatory requirements, reimbursement, and structural implementation in routine care. This article summarises current knowledge on clinical efficacy and safety and discusses the prerequisites for successful implementation in Germany.

Clinical need in severe haemophilia

Severe haemophilia is characterised by spontaneous bleeding, progressive joint damage, and a significant reduction in quality of life. Despite substantial therapeutic advances, such as modern factor concentrates and non-factor-based therapies like emicizumab, a high level of unmet medical need persists. Patients depend on frequent intravenous infusions or subcutaneous injections, requiring consistent treatment adherence. Elevated factor levels are needed to prevent even subclinical bleeds, yet bleeding events still occur despite optimal treatment standards. Chronic arthropathy often leads to work incapacity and severely limits social participation.

The therapeutic goal of a „functional cure", i.e. normalisation of bleeding tendency without regular replacement therapy, has not yet been achieved. Gene therapy offers an innovative approach, enabling endogenous production of the missing clotting factor following a single administration.

The development of gene therapy for haemophilia began in 1993 with the first preclinical attempts. After testing various routes of administration (e.g. intramuscular, intra-arterial), the breakthrough came in 2011 with the first successful AAV-based intravenous gene therapy for haemophilia B. Decades of research ultimately led to the first market approvals: Roctavian® for haemophilia A in 2022 and Hemgenix® for haemophilia B in 2023. In 2024, Beqvez® / Durveqtix® became the third gene therapy to receive FDA and EMA approval for haemophilia B, but following its authorisation, Pfizer chose not to market the product, and de-

velopment was discontinued in 2025. The core principle of currently approved AAV gene therapies is a single intravenous infusion of a modified adeno-associated viral vector that delivers the intact gene for the missing clotting factor, primarily targeting the liver. Subsequent endogenous synthesis of the clotting factor reduces or eliminates the need for regular haemophilia therapy.

Long-term efficacy and safety in haemophilia B

Long-term data on gene therapy for haemophilia B are clinically meaningful: ten men with severe haemophilia B who received a single intravenous infusion of the vector scAAV2/8-LP1-hFIXco showed dose-dependent FIX activity levels ranging from 1.7 to 4.8 IU/dL over an observation period of up to 13 years. Seven of the ten participants did not return to prophylactic replacement therapy and developed a sustained anti-AAV8 capsid-specific antibody response with no relevant safety concerns. [1]

The Phase 3 HOPE-B study with etranacogene dezaparvovec included 54 adult men with a mean age of 41.5 years (range 19-75). 81.5% had severe haemophilia B (<1%), and 18.5% had moderately severe disease (1-2%). After 24 months, 96% of participants remained prophylaxis-free, with a mean FIX activity of 36.7±19.0%. Joint bleeding had disappeared in 60% of patients, and 46.3% no longer required any FIX infusions following gene therapy. [2]

The safety profile was favourable: infusion reactions occurred in 13% (n=7) of participants, and ALT elevations in 18.5% (n=10). These transaminase increases were well controlled with corticosteroid therapy. No serious vector-related adverse events were observed.

Clinical outcomes in haemophilia A

The Phase 3 study of valoctocogene roxaparvovec enrolled 132 men with a mean age of 31.4 years (range 18-70).[3] After five years, the treatment group had a mean FVIII activity of 15.9±2.5 IU/dL, with a median of 6.2 IU/dL.[4] These levels correspond to the range of mild haemophilia. The annualised bleeding rate for treated bleeds decreased by a clinically relevant 88.1%. Over the entire observation period, 81.3% of participants remained free from prophylactic factor replacement. The median annual bleeding rate was zero across all follow-up years.

However, FVIII activity showed considerable interindividual variability. By the end of year four, 24% of participants had FVIII levels below 5 IU/dL, while 52% had levels above 5 IU/dL.[3] This variability underscores the need for individualised treatment advice and management of patient expectation.

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In the GENEr8-1 Phase 3 trial, 90.3% of patients (121 of 134) experienced ALT elevations following treatment with valoctocogene roxaparvovec. Most of these (85.1%) occurred within the first year, with 89% observed during the first 26 weeks.[3] The median time to first ALT elevation was 7 weeks, with a median duration of 4 weeks. Long-term follow-up shows a marked decrease in ALT elevations after year one. In year four, ALT increases occurred in 42.7% of participants, most of which remained below the upper limit of normal. Notably, no corticosteroids were initiated in year four to manage ALT elevations.

Long-term safety and insertional mutagenesis

Molecular safety analyses indicate a low genomic integration rate of AAV vectors. Extensive liver biopsy studies in humans show an integration frequency of only 1-6 events per 1,000 cells genome-wide.[5] More than 99% of sequencing reads represent episomal or concatemeric vector forms, suggesting predominantly non-integrative persistence of the vector. Importantly, no clonal expansion or enrichment near oncogenes has been observed.

In previously reported malignancies (e.g. hepatocellular carcinoma, B-ALL, schwannoma, myelodysplastic syndrome), insertional mutagenesis was ruled out as a cause. Molecular analyses confirmed that these tumours were not induced by AAV insertions, reinforcing the fundamental safety of the approach. Nevertheless, a 15-year follow-up remains essential for long-term safety evaluation.

Structural requirements and regulatory framework

The hub-and-spoke model was developed to ensure access to gene therapy regardless of centre size, experience, or availability of specific consultative services.[6,7] In this model, specialised centres (hubs) determine the indication and perform the gene therapy, while long-term follow-up can be managed by qualified partner institutions (spokes). This approach allows for decentralised care while maintaining high-quality standards. Implementation varies widely across countries, with Germany, France, and the UK each developing their own models.

In 2024, the European Association for Haemophilia and Allied Disorders (EAHAD) updated its accreditation criteria to reflect the demands of new therapies.[8] The revised framework defines structural, procedural, and outcome-based quality requirements for haemophilia centres, including laboratory standards, pharmacovigilance systems, and standardised data collection. Germany introduced its ATMP Quality Assurance Directive in March 2024, setting minimum requirements for treatment centres: they must treat at least 30 patients with severe haemophilia per year, employ a specialist in haemostasis with additional qualifications, and have access to gastroenterological expertise. A structured 15-year follow-up is mandatory.

Follow-up centres must treat at least 10 patients with bleeding disorders per year and participate in a certified quality network.

Implementation and reimbursement challenges

Gene therapy is associated with substantial one-time costs that require innovative reimbursement models. Uncertainty regarding long-term efficacy and interindividual variability necessitates outcome-based agreements. The risk of treatment failure or diminishing effectiveness over time calls for differentiated financing solutions that both recognise the innovation and preserve the sustainability of healthcare systems. The German Society on Thrombosis and Haemostasis (GTH) has issued gene therapy guidelines that consider predictability of outcomes, individual risk profiles, and patient preferences. Particular emphasis is placed on liver health, immune status regarding AAV vectors, and

psychosocial suitability for lifelong follow-up.[9]

Outlook: gene therapy in clinical practice 2025

As of 2025, AAV gene therapy has established itself as a recognised treatment option for adult patients with severe haemophilia without inhibitors. Long-term expression of FVIII and FIX results in significant reductions in bleeding rates, a substantial decrease in factor concentrate usage, and notable improvements in quality of life.

Nonetheless, challenges remain: high one-time costs call for innovative financing and outcome-based contracts. Interindividual variability in factor expression necessitates personalised counselling, and complex reimbursement mechanisms must evolve further. The risk of treatment failure, structural requirements for centres, and the obligation of a 15-year follow-up demand robust networks and close interdisciplinary collaboration.

Future developments will include novel vector systems, optimised gene therapy approaches, and gene editing technologies. Successful implementation will require close integration of clinical expertise, regulatory frameworks, and innovative reimbursement models to ensure access to this transformative therapy for all eligible patients.

Overview of GTH recommendations on gene therapy

Key aspects of gene therapy in haemophilia

- Predictable outcomes, risks, and patient-reported outcomes

Implementation considerations

- Administration and monitoring
- Interdisciplinary collaboration (hepatology and other specialties)

Data management and future

- Use of electronic diaries for data collection and pharmacovigilance
- Reimbursement and future use in adolescents and children

Model SOPs – organisational requirements

- Hub-and-spoke model for treatment centres

Source: (9)

Table 1: The Society of Thrombosis and Haemostasis Research (GTH) has issued recommendations on gene therapy.

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Clinical perspective – Registries in precision oncology

Professor Dr Monika Klinkhammer-Schalke, Professor Dr Sylke Zeißig, Dr Judith Hansinger, Anne Hennings, Bianca Franke

Precision oncology aims to identify the best possible therapy for individual patients based on the molecular characteristics of a tumour and relevant clinical data. A fundamental prerequisite for the use of clinical cancer registries in precision oncology is the Cancer Screening and Cancer Registry Act adopted in 2013 (Krebsfrüherkennungs- und Registergesetz, KFRG, Section 65c of the German Social Code Book V) and the Act on the Consolidation of Cancer Registry Data enacted in 2021. These two legislative measures have led to the nationwide establishment of clinical cancer registries in Germany and have initiated the process of nationwide consolidation and analysis of clinical cancer registry data, thereby providing transparency regarding the care of people affected by cancer.[1] A further prerequisite for the use of registries in precision oncology is the documentation of diagnostic and therapeutic procedures performed, including the respective follow-up, based on the standardised oncological core dataset (uniform oncological basic dataset, oBDS), which is legally mandatory for all reporting physicians (Section 65c of the German Social Code Book V).[2,3]

Background: Nationwide implementation and use of clinical cancer registries in Germany

In the context of establishing the two legislative initiatives adopted in 2013 and 2021 to enable the use of population-based, nationwide clinical registry data to improve transparency in patient care, the oBDS was also defined by law. It constitutes the basis for all oncological procedures that are subject to mandatory reporting to the respective clinical cancer registries in the federal states.[2,3] This dataset and the associated follow-up can also be used to describe care processes and outcome quality in precision oncology.

To obtain more detailed information on the outcomes of patients who have received systemic therapy, it is often necessary to link data from other sources (e.g. routine data on comorbidities) with clinical cancer registry data. As this has not yet been possible as a standard approach in Germany – partly due to the absence of a uniform identifier – the Act on the Consolidation of Cancer Registry Data introduced a concept for a so-called Platform Level 2 (PLATO 2). This platform is intended to enable „nationwide, event-driven consolidation and analysis of cancer registry data from the federal states, as well as linkage of cancer registry data with other data sources, and to promote the clinical and scientific evaluation of cancer registry data“ (Section 10, sentence 2, Federal Cancer Registry Data Act [Bundeskrebsregisterdatengesetz, BKRG]).

This concept was developed jointly by the Association of German Tumour Centres (Arbeitsgemeinschaft Deutscher Tumorzentren, ADT), the German Cancer Society (Deutsche Krebsgesellschaft, DKG), the German Cancer Aid (Deutsche Krebshilfe), the clinical cancer registries pursuant to Section 65c of the German Social Code Book V, the Centre for Cancer Registry Data (Zentrum für Krebsregister-


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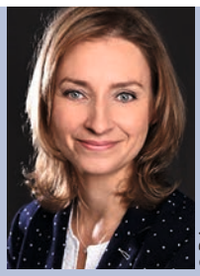
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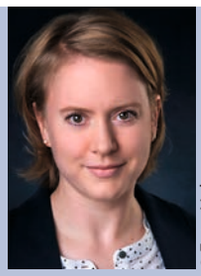
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is a physician and theologian and heads the Centre for Quality Assurance and Health Services Research at the University of Regensburg. In addition, as Past President of the Association of German Tumour Centres (Arbeitsgemeinschaft Deutscher Tumorzentren, ADT), she leads the cross-cutting working group on quality and networking within the National Cancer Plan. In recognition of her commitment, she was awarded the German Cancer Prize in 2025 by the German Cancer Society and the German Cancer Foundation.

Professor Dr Sylke Zeißig
has extensive expertise in cancer epidemiology and health services research. Since 2024, she has served as Chair of the Association of German Tumour Centres (ADT). Through a joint professorship in Würzburg, she combines the directorship of the Würzburg Regional Centre of the Bavarian Cancer Registry with a professorship in Clinical Epidemiology of Cancer at the Institute of Clinical Epidemiology and Biometry (IKE-B) at the University of Würzburg.

Anne Hennings
has been Research and Communications Officer at the Association of German Tumour Centres (ADT) since 2022. In this role, she coordinates the „Platform Level 2 (PLATO 2)" project, which supports the further development of health data use in oncological research and healthcare delivery. Prior to this, from 2011 to 2021, she worked as a research associate and, from 2018 onwards, as head of office in the parliamentary office of former Federal Minister Dr Gerd Müller, Member of the German Bundestag (MdB).

Dr Judith Hansinger
is a specialist in paediatrics and adolescent medicine with extensive experience in clinical care, medical leadership, and scientific research. Since November 2025, she has been working as a research associate and physician at the Association of German Tumour Centres. Previously, from 2022 to 2025, she was responsible for health services research as a physician at the Centre for Quality Assurance and Health Services Research at the University of Regensburg. Her clinical experience includes work in paediatric practices and hospitals, including a period in a medical leadership role, as well as completion of full specialist training.

Bianca Franke
is an economist who studied at Humboldt University of Berlin. Since 2008, she has headed the executive office of the Association of German Tumour Centres (ADT), following earlier roles in corporate controlling and consultancy. In this position, she is responsible for the nationwide Oncology Quality Conference of the ADT and coordinates projects such as the further development of the oBDS and the Cancer Research Data Centre project (onkoFDZ).

Systemic therapy in the uniform oncological basic dataset

Number	16.3
Group	Systemic therapy
Field name	Type of systemic or watchful strategy
Definition	Indicates which type of therapy or watchful strategy was applied
Categories	CH = Chemotherapy HO = Hormone therapy IM = Immuno-/antibody therapy ZI = Targeted substances CI = Chemotherapy and Immuno-/antibody therapy CZ = Chemotherapy and targeted substances CIZ = Chemotherapy and Immuno-/antibody therapy + targeted substances IZ = Immuno-/antibody therapy + targeted substances SZ = Stem cell transplantation (including bone marrow transplantation) AZ = Active surveillance WS = Wait and see WW = Watchful Waiting SO = Other
Notes	Antibody therapy (-mab) should be reported under IM; all other targeted substances should be reported under ZI. In the technical implementation, only one type of therapy can be recorded per systemic therapy entry. Wait and see should only be reported if foreseen in the guideline or therapeutic concept, and not during treatment breaks.

Source: www.basisdatensatz.de

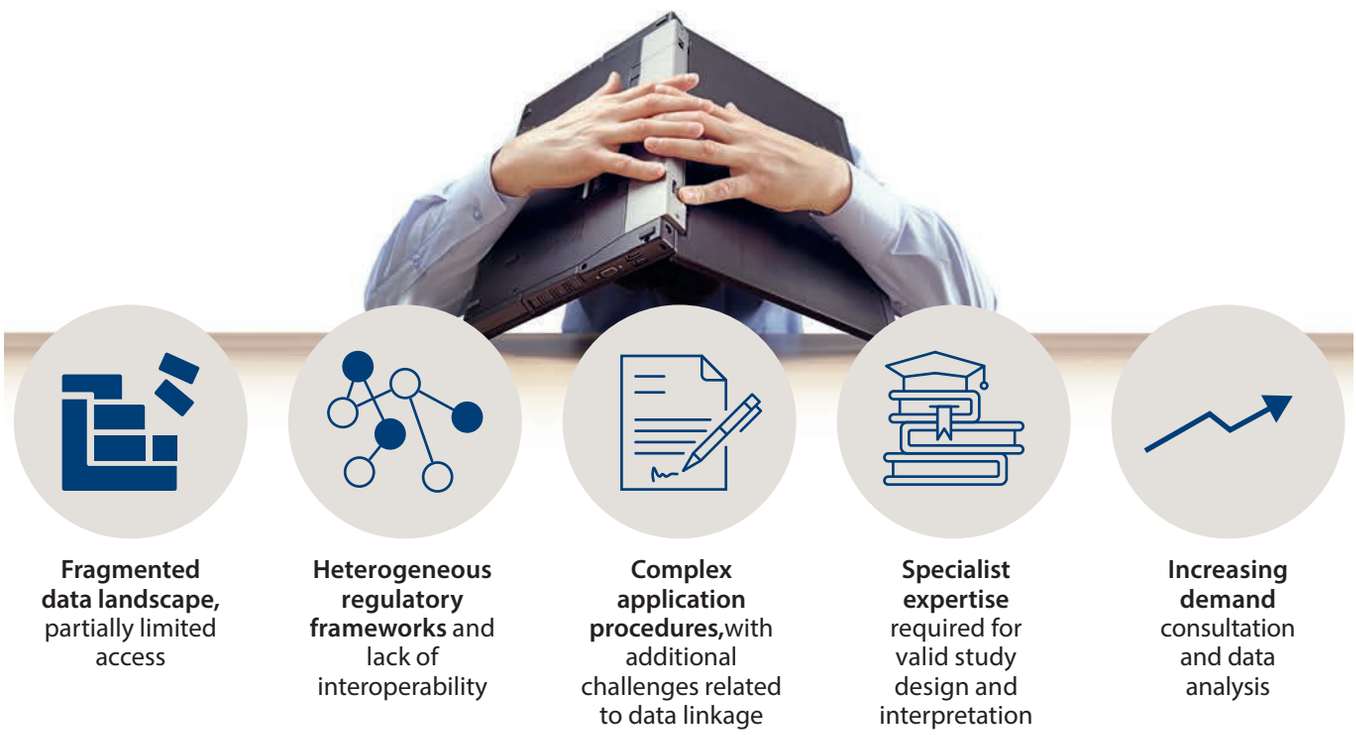
Figure 1: The uniform oncological basic dataset (oBDS) forms the basis for all oncological procedures that are subject to mandatory reporting to the respective clinical cancer registries in the federal states.

daten, ZfKD) at the Robert Koch Institute, and patient self-help organisations within the German Cancer Self-Help Association. It was submitted to the Federal Ministry of Health on 7 May 2025.

Need for a platform enabling broad data use

Numerous relevant data sources currently exist within separate infrastructures. Foremost among these are the statutory clinical cancer registries, which ensure nationwide documentation of diagnoses, therapies and disease trajectories and thus form the basis for quality assurance and analyses of healthcare delivery. Of central importance for precision oncology are, in addition, molecularly oriented initiatives such as the National Network for Genomic Medicine (Nationales Netzwerk Genomische Medizin, nNGM), the Centres for Personalised Medicine (Zentren für Personalisierte Medizin, ZPM) within the German Network for Personalised Medicine (Deutsches Netzwerk für Personali-

Challenges: fragmented data landscape and data linkage



Source: ADT Network for Healthcare Delivery, Quality and Research, Berlin © Brian Jackson / stock.adobe.com

Figure 2: To date, it is often difficult to link other data sources (e.g. routine data on comorbidities) with clinical cancer registry data, in part due to the absence of a uniform identifier.

sierte Medizin, DNPM), as well as the nationwide platform for medical genome sequencing, genomDE. Furthermore, billing data from statutory and private health insurances play an important role, as they reflect real-world care and cost structures. This landscape is complemented by additional research initiatives such as the Network University Medicine (Netzwerk Universitätsmedizin, NUM), the Medical Informatics Initiative (Medizininformatik-Initiative, MII), specialised oncological registries focusing on specific tumour entities or treatment modalities, and data from population registration offices. An increasingly important resource is also represented by large population-based cohorts with prospective follow-up, most notably the German National Cohort (NAKO Health Study).

In contrast, there is an active oncology research community whose primary focus lies on clinical trials, alongside health services research and basic oncological research. This focus, together with limited possibilities for data link-

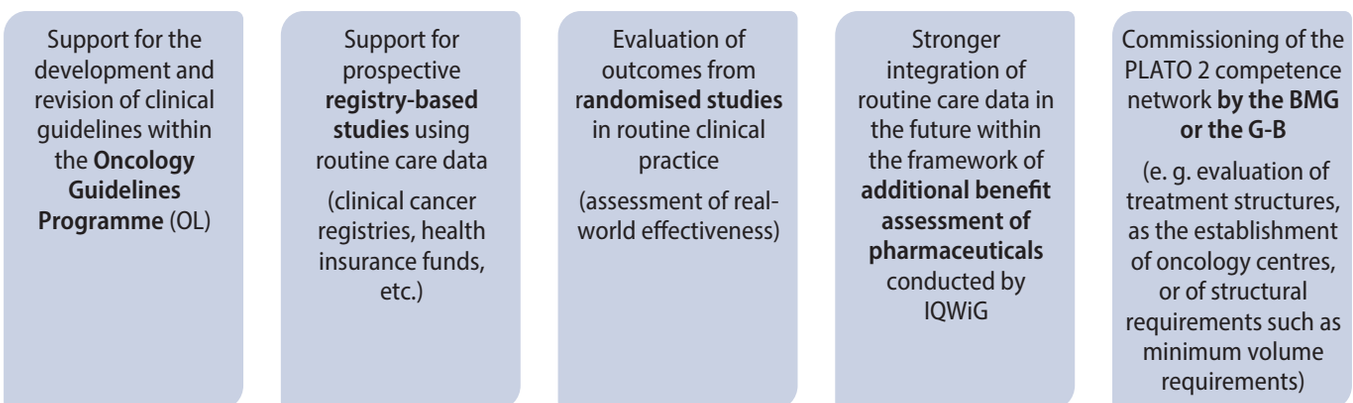


Figure 3: The Platform Level 2 (PLATO 2) aims to connect existing and newly emerging data infrastructures through consultation and support in such a way that they can be used efficiently for research purposes.

age, has resulted in comparatively low research utilisation of the existing data resources. Low-threshold access to data and the integration of clinical and methodological expertise are essential prerequisites for an evidence-based, „learning" healthcare system.

PLATO 2 is intended to enable this.[4]

For most clinical and health services research questions, it is necessary to integrate data from multiple sources. This approach should become standard practice in oncological research, as it also helps to avoid duplicate documentation.[4]

The Platform Level 2 solution

The Platform Level 2 (PLATO 2) aims to connect existing and newly emerging data infrastructures through consultation and support in such a way that they can be used efficiently for research purposes. This is intended to substantially enhance opportunities for the use of existing data in the development of clinical guidelines, registry-based studies, additional benefit assessments, and the analysis of randomised studies conducted within routine clinical care.[4]

Competence network and coordination office

The complex structure of existing data sources requires competent support and governance. Each data resource offers specific opportunities but is also associated with its own limitations. The preparation of data access applications for the various data sources can be significantly facilitated by the involvement of experienced experts who are familiar both with the specific characteristics of the data landscape and with current and relevant research questions in oncology.

The core concept of the PLATO 2 competence network is to retain data sovereignty with the respective data holders. Data are not centralised; instead, they are brought toge-

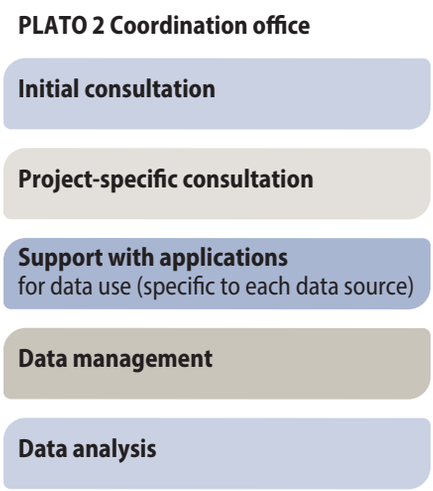
ther in a purpose-driven and research-question-specific manner within the institutions designated for this purpose.[4] The PLATO 2 competence network would provide advice on the specification of research questions and optimise their operationalisation using the available data. It would support the selection of the required data sources, moderate the necessary coordination processes between stakeholders where needed and mandated, facilitate and accelerate application procedures, and connect researchers with suitable infrastructure partners responsible for the required data processing and linkage.[4]

The organisation and governance of these advisory processes would be assumed by a coordination office of the competence network, serving as an externally visible point of contact and hosted by the ADT. Through its members, the ADT already brings together key partners within the oncology landscape as a network (including Comprehensive Cancer Centres, organ-specific cancer centres and other oncology centres, cancer registries and universities) and maintains close links with oncological professional societies, various working groups, the certification system of the German Cancer Society, and the Oncology Guidelines Programme.[5]

In addition, the ADT has many years of experience in the analysis of routine care data (Versorgungsnahe Daten, VeDa) in oncology through the establishment of the nationwide Oncology Quality Conference, the results of which have traditionally been presented for the first time at the German Cancer Congress.

Since 2006, this ADT project has brought together oncological entities nationwide, initially focusing on breast and colorectal cancer, and has analysed them on the basis of established quality indicators or other specific clinical research questions. To mark the 20th anniversary of the Oncology Quality Conference, results from analyses of 21 tumour entities will be presented at the German Cancer Congress in 2026.

Tasks of the coordination office



Source: ADT Network for Healthcare Delivery, Quality and Research, Berlin

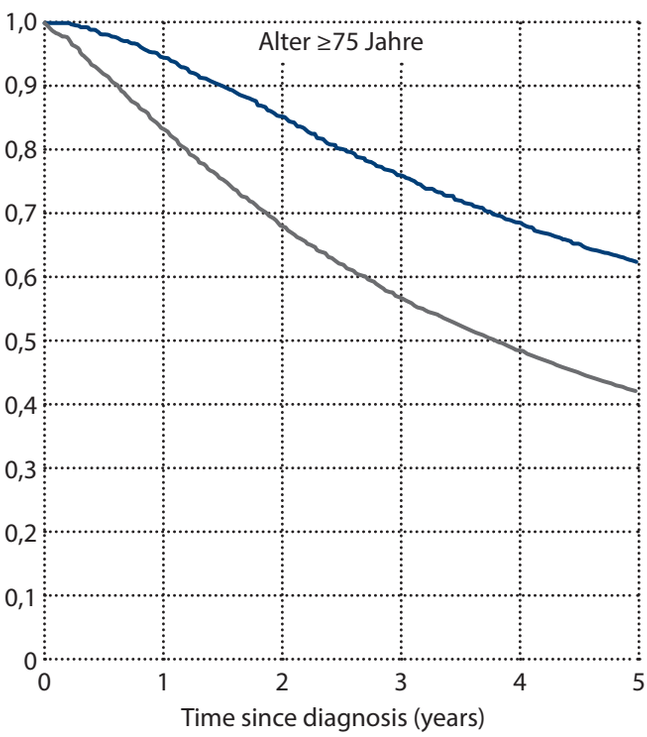
Figure 4: The organisation and governance of the advisory processes are assumed by a coordination office of the competence network, which serves as an externally visible point of contact.

These analyses are reviewed, discussed, and finalised for publication within an inter- and multidisciplinary team comprising clinicians, representatives of cancer registries, statisticians and health services researchers.

A key objective is, on the one hand, to demonstrate the implementation of recommended clinical guideline recommendations in routine care and, on the other hand, to make more intensive use of population-based, nationwide and longitudinal data from clinical cancer registries and other data sources for analytical purposes. There is a substantial need to better utilise such routine care data to address open questions in clinical guidelines, particularly in

Overall survival following adjuvant chemotherapy in patients aged ≥ 75 years

Cumulative survival (14,449 patients with stage III colon cancer according to UICC classification; mean overall follow-up: 11.4 years)



Survival benefit following adjuvant chemotherapy was also observed in patients aged over 75 years in univariate analysis. After risk adjustment in multivariable analysis, a clear improvement in overall survival following adjuvant chemotherapy was likewise demonstrated:

Adjuvant chemotherapy:	p-value	HR	Lower 95 %	Upper 95 %
No		1.00		
Yes	<0.01	0.672	0.640	0.706

Source: ADT Network for Healthcare Delivery, Quality and Research, Berlin

Figure 5: Population-based analyses make it possible to assess the effectiveness of therapies in patient groups that are generally not represented in randomised studies due to inclusion criteria, illustrated here by overall survival following adjuvant chemotherapy in patients aged over 75 years with stage III colon cancer.

areas where no randomised controlled trials are available as an evidence base.

This applies in particular to the effectiveness of recommended therapies in older patients, as outcomes in this population are often not adequately captured in randomised studies due to restrictive inclusion criteria and the higher likelihood of comorbidities.

Results from population-based analyses reflecting broad implementation of therapies in routine care, including in older patients, have demonstrated a clear overall survival benefit, illustrated for example by postoperative adjuvant chemotherapy in stage III colon cancer.

In addition, the outcome quality of structural innovations[6] can be assessed on the basis of analyses combining

multiple data sources, as demonstrated by the study „Effectiveness of Certified Centres“ (Wirksamkeit zertifizierter Zentren, WIZEN), which linked registry data with health insurance claims data.[7]

Outlook

Routine care data and the linkage of different data sources create transparency in healthcare delivery, particularly with regard to:

- the general population,
- an ageing society, enabling improved knowledge about older people,
- rare cancers and secondary malignancies following oncological treatment in childhood,
- the prognostic and therapeutic relevance of molecular markers and genetic information,
- personalised therapies and their benefit.

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Routine practice data collection: A critical review

Dr Florian Jantschak | Department of Pharmaceuticals at the National Association of Statutory Health Insurance Physicians (KBV)

The Act for Greater Safety in the Supply of Pharmaceuticals (GSAV) introduced routine practice data collection for pharmaceuticals with weak approval evidence. In particular, the aim was to generate a more robust evidence base for a subsequent benefit assessment of orphan drugs through downstream data collection. However, since 2020, only five routine practice data collection procedures have actually been implemented. Challenges include lengthy procedural timelines, a limited number of eligible patients, the lack of suitable registries, high requirements for data quality, and the generally limited informative value of non-randomised studies. The expected improvement in evidence is unrealistic, and the potential for cost reduction is low. The routine practice data collection procedure should be discontinued in the long term, as it is neither efficient nor effective. Instead, orphan drugs should should be subject to a regular benefit assessment. The insights gained from routine practice data collection procedure so far can nonetheless help optimise study designs and improve registry quality.

On 16 August 2019, the Act for Greater Safety in the Supply of Medicines (GSAV) came into force. An amendment to Section 35a (3b) of the German Social Code Book V (SGB V) authorises the Federal Joint Committee (G-BA) to require the submission of routine practice data collection for the purpose of (re-)assessing the additional benefit of pharmaceuticals used to treat rare diseases (orphan drugs), pharmaceuticals with a conditional marketing authorisation (CMA), and those authorised under exceptional circumstances (MAEC). The focus is on observational studies, case-control studies, and registry studies. Randomised controlled trials (RCTs) are excluded.[1]

If, after the implementation of an routine practice data collection, the additional benefit of an orphan drug still cannot be quantified based on the data collected, a further amendment to Section 130b (3) of the German Social Code Book V (SGB V) allows the National Association of Statutory Health Insurance Funds (GKV-SV) to negotiate a discount on the reimbursement amount initially agreed during the first benefit assessment. In the case of a standalone conditional marketing authorisation (CMA) or marketing authorisation under exceptional circumstances (MAEC), renewed price negotiations are also conducted.

To ensure the collection of complete and valid real-world data from statutory health insurance (SHI) care, the Federal Joint Committee (G-BA) may restrict the prescribing of the relevant pharmaceuticals at the expense of the SHI to healthcare providers who participate in the mandated routine practice data collection.

The legislator defined the following objectives for this regulatory amendment:

1. Pharmaceuticals that have been approved based on limited evidence, particularly orphan drugs, should remain

promptly accessible to patients covered by the SHI system, while at the same time generating a stronger evidence base for a (re-)assessment of their additional benefit.
2. The aim is to create incentives for conducting routine practice data collections, while also avoiding situations where the reimbursement amount remains permanently high despite a lack of sufficient evidence of additional benefit[1] Thus, the routine practice data collection is to be regarded both as a tool for generating better evidence and as an instrument of price regulation.

Since the statutory assumption of additional benefit for orphan drugs under Section 35a (1) sentence 11 constitutes an exemption from the regular benefit assessment, the routine practice data collection can also be seen as a corrective special provision within this exemption.


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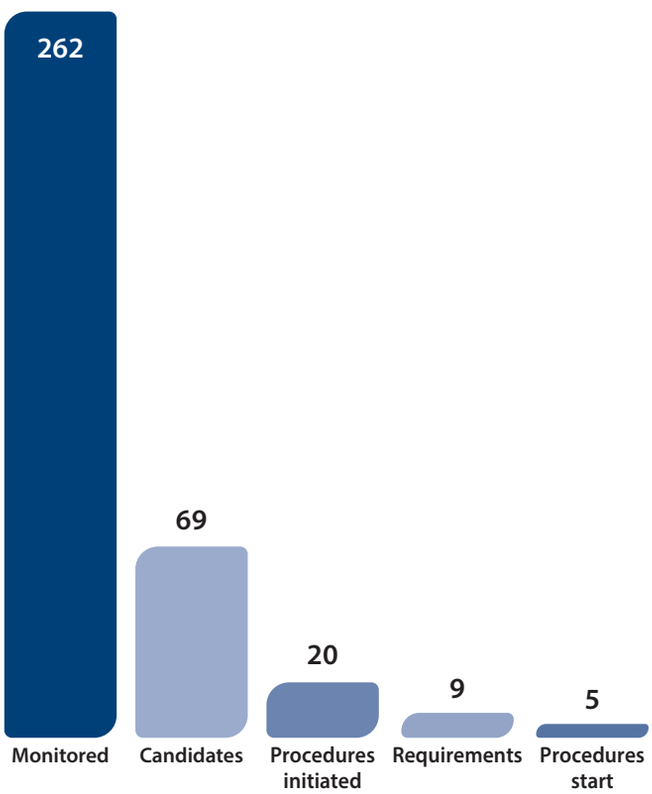
Status of Application-Related Data Collection Procedures at the G-BA

Since March 2020, the Federal Joint Committee (G-BA) has been reviewing ongoing marketing authorisation procedures at the European Medicines Agency (EMA) to determine whether the respective pharmaceuticals are suitable for routine practice data collection, in accordance with the legal requirements. Publicly available information from authorisation procedures and clinical trial registries is generally used for an initial screening. If no RCT data is available within the authorisation procedure, it is typically assumed that the evidence base is insufficient for a later benefit assessment.[2]

Between March 2020 and March 2025, based on the monitoring of 262 active substances, a total of 69 marketing authorisation procedures were identified for pharmaceuticals with an orphan designation and/or a potential conditional marketing authorisation (CMA) or marketing authorisation under exceptional circumstances (MAEC), which were based on single-arm clinical trials. In these cases, routine practice data collection was generally considered necessary (figure 1). These authorisation procedures formed the pool of candidates to be assessed and discussed by the G-BA.

Selection is made on a case-by-case basis and, according to Section 54 (2) of the G-BA's Rules of Procedure (VerfO), takes into account the feasibility and appropriateness of data collection. This may involve a search for existing registries in the relevant therapeutic area. In addition, an estimate is made as to whether the therapeutic area in question involves a particularly small patient population. The G-BA follows a threshold proposed by the Institute for Quali-

Key figures on the data collection procedure



Source: internal data (monitored active substances and candidates) and resolutions of data collections; own presentation

Figure 1: Number of routine practice data collection procedures since March 2020 (as of 18 April 2025). Only five out of 262 monitored pharmaceuticals have been subject to such a procedure so far.

ty and Efficiency in Health Care (IQWiG), according to which an adjusted indirect comparison is considered methodologically feasible starting from a population of 100 patients.[2,3]

An appropriate comparator therapy is also defined, which forms the basis for discussions on potential comparators. Pharmaceutical candidates in therapeutic areas without available alternatives are generally not pursued further.

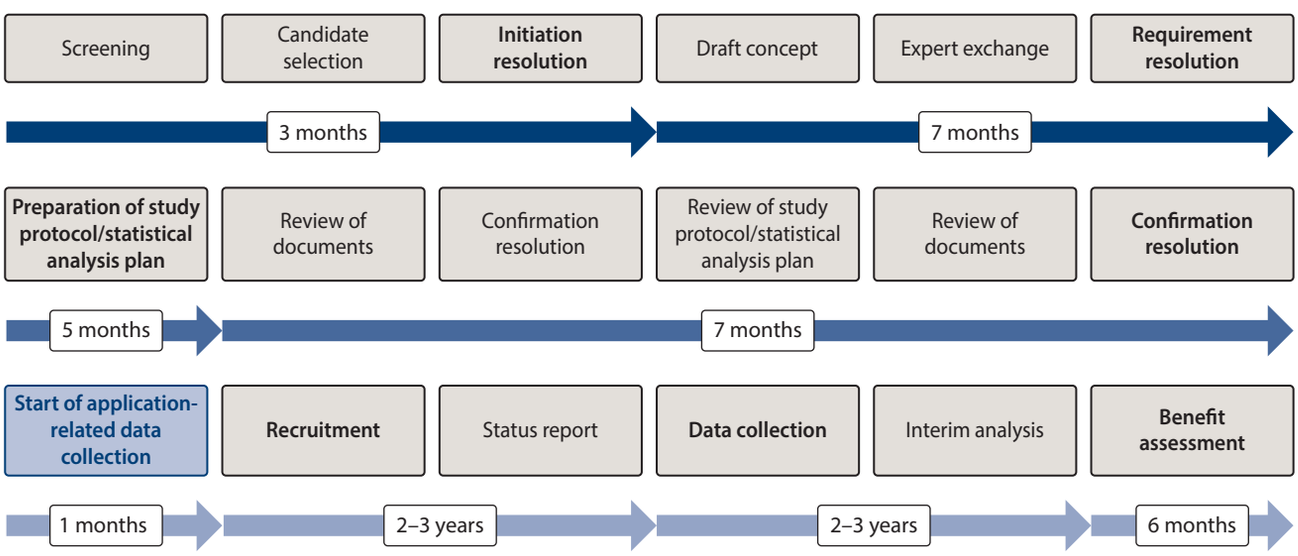
If a candidate is considered potentially suitable, the G-BA adopts a resolution to initiate the procedure, and IQWiG is commissioned to develop a concept for routine practice data collection. A second resolution formally mandating the data collection is passed following expert consultations with registry holders, the pharmaceutical companies involved, clinical experts, and representatives from the Federal Institute for Drugs and Medical Devices (BfArM) or the Paul-Ehrlich-Institut (PEI).

Of the 69 candidates identified, 20 routine practice data collection procedures have been initiated to date. In nine of these cases, the G-BA was able to mandate data collection. In two cases, the procedure was discontinued after the pharmaceutical companies failed to submit a study protocol (SP) and a statistical analysis plan (SAP). In one case, the legal basis ceased to apply following the granting of marketing authorisation (figure 1, table 1, table 2). For eight pharmaceuticals with initiated procedures, parallel RCTs were ongoing in earlier lines of therapy. Seven of these were brought to market with a CMA.

As of 20 March 2025, around six years after the GSAV came into effect, only five routine practice data collection procedures have begun gathering real-world data on the use of the respective pharmaceuticals in Germany.

The duration of a routine practice data collection procedure from the point of the formal mandate to the new resolution on the assessment of additional benefit currently averages around 6.5 years (81 months). This includes the preparation of the SAP and SP by the pharmaceutical company, review by IQWiG, registry adaptation, recruitment,

Overview of the routine practice data collection procedure



Source: Resolutions of routine practice data collections and procedural rules of the G-BA; own presentation

Figure 2: Routine practice data collection is a lengthy and administratively complex process. The total duration from candidate selection to the final benefit assessment can take up to eight years.

and data collection, as well as the subsequent benefit assessment. An additional ten months must be anticipated for the preceding candidate selection process (figure 2, table 1). Extensions are possible if, for instance, more time is needed to recruit the required number of patients. Legally, routine practice data collection can be mandated at the earliest from the time of market availability in Germany.

Evidence base and potential for routine practice data collection for orphan drugs in the AMNOG procedure

A total of 217 benefit assessments for orphan drugs initiated between 2020 and 2024 were identified in the AMNOG database available on the G-BA's website. The analysis included those procedures in which the G-BA conducted a dossier assessment under the statutory assumption of additional benefit and for which a resolution had been adopted by 20 March 2025. This selection provides a good representation of the evidence base at the start of availability in Germany and included orphan drugs for which the implementation of routine practice data collection could have been considered. A total of 93 benefit assessment procedures were included in the present analysis. Of these, 31 involved oncological indications and 62 related to non-oncological therapeutic areas.

Overall, 60 out of 93 procedures included data from ran-

domised controlled trials (RCTs). RCTs were conducted more frequently in non-oncological therapeutic areas than in oncological ones. However, in only 26 of the 60 RCT-based procedures could the additional benefit be quantified. In a further 11 RCT-based assessments, the G-BA was able to identify a benefit at the level of individual endpoints. In three cases, only disadvantages were observed despite the presence of RCT data. In total, the additional benefit could not be quantified in 66 out of 93 cases. In 33 of these procedures, no data suitable for the benefit assessment were available at all. In 52 out of 93 cases, the additional benefit was determined solely on the basis of the statutory assumption of additional benefit. In only one case was the additional benefit quantified in the absence of RCT data (atidarsagene autotemcel).

According to the published resolution documents, 33 procedures involved a particularly small patient population of fewer than 100 patients. For this analysis, the lower end of the stated patient range was used to conservatively identify therapeutic areas with very small populations. In therapeutic areas with multiple subpopulations, patient numbers were aggregated.

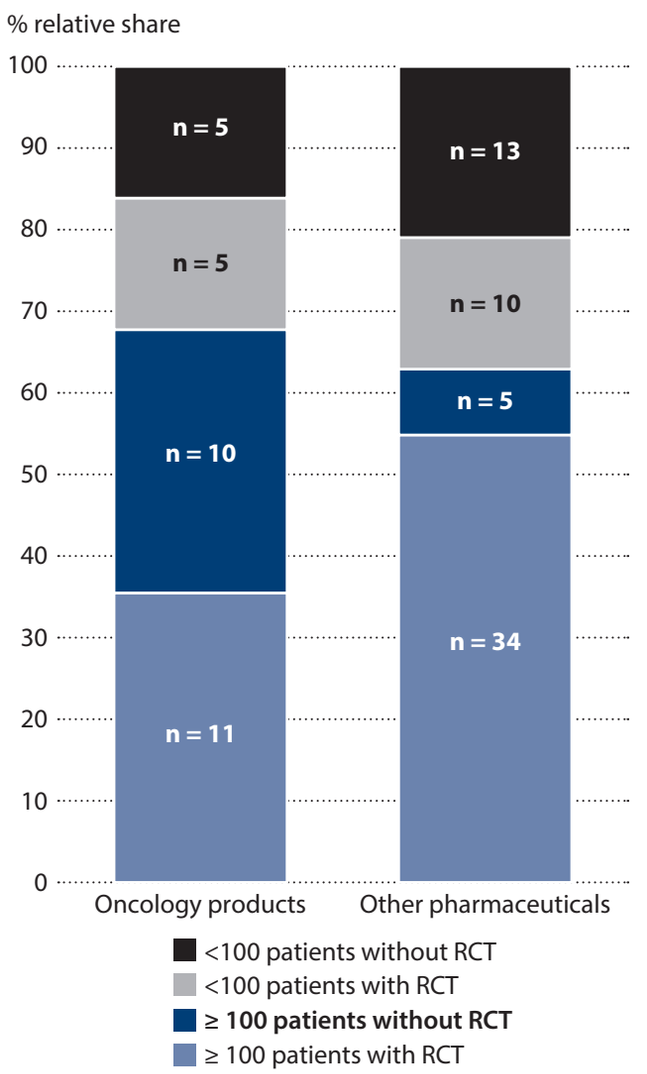
Only 15 of the 93 assessed orphan drugs fulfilled two key criteria for routine practice data collection: no RCT data were available for the assessment, and the therapeutic area comprised more than 100 patients (figure 3) Among this group, routine practice data collection procedures were initiated for six products.

Practical limitations of implementing routine practice data collection procedures

• Long procedureal timelines

One of the core issues with routine practice data collection is its lengthy implementation timeline. Particularly in dynamic therapeutic areas, there is concern that the data collec-

The potential for routine practice data collection in orphan drugs



Source: G-BA benefit assessment resolutions; own presentation

Figure 3: Benefit assessments initiated between 2020 and 2024. Only 15 out of 93 assessed orphan drugs met both key criteria for data collection: patient population above 100 and no available RCT.

ted may no longer be relevant to actual clinical practice by the time the additional benefit is assessed.

The EMA often takes an adaptive approach in authorisation procedures for oncology indications. A pharmaceutical product may initially be granted a conditional marketing authorisation (CMA) for a narrowly defined patient population with high unmet medical need, based on early clinical data. At the same time, a Phase III RCT in an earlier line of therapy may already be underway, and the product is likely to receive approval and be used in this new treatment setting in the medium term.[5,6] This raises the question of whether data from application-related data collection, which addresses only the initially approved indication, will still be relevant for future clinical care. A particularly critical scenario arises if the data collection cannot be completed, based on currently observed timelines, until higher-quality evidence from the earlier treatment line is already expected to become available.

There is also a risk that the comparators specified in the formal mandate may no longer reflect the current state of medical knowledge at the time of the later benefit assessment. While it is generally possible to adapt the choice of comparators during the course of data collection, removing a comparator to which a relevant proportion of already recruited patients has been assigned can be problematic. Newly added comparators, in turn, are subject to a shortened data collection period.

• Very large effect sizes required

In methodologically sound comparative studies without randomisation, the Institute for Quality and Efficiency in Health Care (IQWiG) requires that conclusions about the benefit or harm of an intervention can only be drawn if the 95% confidence interval for an observed effect on endpoints in the category of serious or severe complications exceeds a relative risk threshold of 2 to 5.[7]

While this threshold is below that of a „dramatic effect", application-related data collection, based on a shifted null hypothesis, is generally only sensitive enough to detect very large effect differences in patient-relevant endpoints. Such large effects become increasingly unlikely the more effective the available comparator therapies are.

This presents an obvious dilemma: routine practice data collection is intended precisely for pharmaceuticals lacking sufficient evidence of additional benefit, in order to justify lower reimbursement amounts. A conventional sample size calculation, as would be used in a clinical trial to confirm a superiority hypothesis, reaches its limits in the context of routine practice data collection. Moreover, there is uncertainty as to how a treatment effect with varying degrees of magnitude should be categorised according to the benefit categories defined in Section 5 (7) of the Regulation on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

• Even established registries require adaptation before use

For the implementation of routine practice data collection, it is advantageous to rely on an existing disease-specific registry that already collects patient-relevant endpoints and captures a substantial portion of the target population. However, even well-established registries have so far only been considered suitable data sources if significant adaptations were made.

During the development of data collection concepts, IQWiG repeatedly criticised that patient-reported outcomes and adverse events were not collected to a sufficient extent, that baseline data lacked important confounders needed for indirect comparisons, and that quality assurance measures such as source data verification were inadequate.[8,9] Difficulties may arise when the absence of a suitable

Overview of active routine practice data collection procedures and their durations

Active ingredient and trade name/Authorisation status	Indication Substance class	Decision date	Reason for discontinuation
Onasemnogen – Zolgensma® Orphan drug and CMA	Spinal muscular atrophy ATMP: Gene therapy	Requirement: 04 February 2021 Start: 01 February 2022	01 July 2027 Duration: 83 months
Risdiplam – Evrysdi® Former orphan drug	Spinal muscular atrophy Small molecule	Requirement: 21 July 2022 Start: 30 October 2024	01 April 2028 Duration: 74 months
Brexucabtagen – Tecartus® Orphan drug and CMA	MCL from third line ATMP: CAR-T-cells	Requirement: 21 July 2022 Start: 21 August 2023	21 July 2028 Duration: 78 months
Valoctocogen – Roctavian® Orphan drug and CMA	Severe haemophilia A ATMP: Gene therapy	Requirement: 02 February 2023 Start: 30 August 2024	02 November 2029 Duration: 87 months
Etranacogen – Hemgenix® Orphan drug and CMA	Severe haemophilia B ATMP: Gene therapy	Requirement: 12 May 2023 Start: 30 August 2024	02 November 2029 Duration: 84 months
Fidanacogen - Beqvez® CMA	Severe haemophilia B ATMP: Gene therapy	Requirement: 18 April 2024 Not yet marketed	Open
Exagamglogen - Casgevy® Orphan Drug and CMA	Severe sickle cell disease ATMP: Gene therapy	Requirement: 21 December 2023 Start: Open	Open

Overview of active routine practice data collection (as of 18 April 2025)
ATMP = Advanced Therapy Medicinal Product, CMA = Conditional Marketing Authorisation, MCL = Mantle Cell Lymphoma

Source: G-BA resolutions on routine practice data collection

Table 1: In dynamic therapeutic areas, there is a risk that data collected may no longer be relevant for care at the time of the benefit assessment due to the long procedural timelines.

registry leads to a decision not to mandate routine practice data collection, despite an insufficient evidence base. In such cases, equal treatment considerations may later require the initiation of data collection once a registry becomes available, particularly if routine practice data collection is then being discussed for a newly authorised pharmaceutical in the same therapeutic area.[10] This may become problematic in terms of proportionality, especially when data collection is expected for a pharmaceutical that has already been firmly established in routine care for several years.

- **High administrative effort**

Routine practice data collection is associated with a high administrative burden. This is primarily due to the extensive requirements regarding data volume and data quality.

Although the legislator stipulated that data collection should take place alongside routine clinical use and that prescribing physicians should not be subject to restrictions in terms of pharmaceutical supply (i.e. no randomisation or study-specific protocols), the data collection must nevertheless be conducted for the purpose of benefit assessment.[11]

The collection of patient-reported outcomes, in particular, entails considerable personnel and logistical effort. This is compounded by the narrow time windows in which data must be collected for each individual patient.11,12 In addition, the requirements for source data verification pose challenges for both registry operators and healthcare providers.[12]

Since the data generated, at the expense of the pharmaceutical company, must be considered in the subsequent benefit assessment under Section 7 (2a) of the Regulation on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), extensive review and consultation of each routine practice data collection project is required in advance by the G-BA. IQWiG, in turn, commits significant resources to the development of data collection concepts and to the review of study protocols and statistical analysis plans.

Where possible, a joint routine practice data collection should be conducted for several new pharmaceuticals in the same therapeutic area. Data collection using a master protocol within the same registry or platform study, with a shared control group, can reduce both effort and costs.[13] However, in cases where data collection is tied to a prescribing restriction for multiple products within the same therapeutic area, a pharmaceutical company that refuses to participate and instead seeks a new price negotiation with the GKV-SV may gain a competitive advantage over others who generate additional evidence.

• Overestimation of the available patient population

The estimated number of patients eligible for data collection is usually determined by IQWiG in its routine practice data collection concept, based on publicly available information, particularly taking into account prior G-BA benefit assessment resolutions. However, population size calculations are regularly subject to high levels of uncertainty. Without robust data on the expected effectiveness of a new pharmaceutical in terms of patient-relevant outcomes, it is also difficult to estimate the required sample size. Moreover, the future demand for a new pharmaceutical in actual clinical practice remains uncertain.

In three cases, within the indications of follicular lymphoma and acute lymphoblastic leukaemia, procedures had to be discontinued because the number of patients who could realistically be recruited in practice was expected to be significantly lower than the number estimated by IQWiG, according to the assessments of clinical experts and registry operators.[14,15]

Conclusions

The routine practice data collection has not met expectations. The legislator originally assumed that around nine to ten such procedures would be mandated and implemented by the G-BA each year.[1] After five years of practical experience, it has become clear that the feasibility and appropriateness of data collection can often be questioned in advance. Even in its early stages, the procedure was regarded merely as a stopgap solution in individual cases.[16] The German Council of Experts on Health and Care (SVR) also concluded in its 2025 annual report that routine practice data collection, in its current form, must be considered fundamentally dysfunctional.[17]

The number of suitable candidates is low, as most orphan drugs are supported by RCT data sufficient for bene-

Overview of discontinued routine practice data collection procedures

Active ingredient and trade name/Authorisation status	Indication Substance class	Decision date	Reason for discontinuation
Fedratinib – Inrebic® Orphan drug	ALL from third line ATMP: CAR-T-cells	Initiation: 21 October 2021 Requirement: 03 November 2022 Termination: 01 June 2023	Opt-out by pharmaceutical company Following the requirement for a routine practice data collection, no study protocol or SAP was submitted.
Brexucabtagen – Tecartus® Orphan drug and CMA	ALL ab Zweitlinie ATMP: CAR-T-Zellen	Initiation: 03 November 2022 Termination: 20 July 2023	Severely limited recruitability in clinical practice. Smaller effect sizes than expected in the concept.
Exagamglogen – Casgevy® Orphan drug and CMA	Beta-thalassaemia ATMP: Gene therapy	Initiation: 06 July 2023 Termination: 01 February 2024	Only a restricted indication was approved. Target sample size for adequate confounder control could not be achieved.
Marstacimab – Hympavzi® Regular authorisation	Severe haemophilia or B Monoclonal antibody	Initiation: 04 April 2024 Termination: 05 December 2024	No authorisation as an orphan drug and no conditional marketing authorisation. No legal basis for requiring an a routine practice data collection.
Epcoritamab – Tepkinly® CMA	FL from third line Bispecific antibody	Initiation: 04 April 2024 Termination: 06 March 2025	Registry operators stated that only 80–90 patients in the target population could be recruited within three years.
Odronextamab – Ordspono® Orphan drug and CMA	FL from third line Bispecific antibody	Initiation: 01 February 2024 Termination: 06 March 2025	Registry operators stated that only 80–90 patients in the target population could be recruited within three years.
Iptacopan – Fabhalta® Orphan drug	Paroxysmal nocturnal haemoglobinuria Small molecule	Initiation: 01 August 2024 Termination: 20 March 2025	Due to its structure and contractual framework, the IPIG registry established within the indication is unsuitable for routine practice data collection.
Talquetamab – Talvey® Orphan drug and CMA	MM from fourth line Bispecific antibody	Initiation: 19 October 2023 Requirement: 18 July 2024 Termination: 17 April 2025	Opt-out by pharmaceutical company Following the requirement for an application-related data collection, no study protocol or SAP was submitted.

Overview of discontinued routine practice data collection (as of 18 April 2025)
ALL = Acute lymphoblastic leukaemia, CMA = Conditional marketing authorisation, FL = Follicular lymphoma, MM = Multiple myeloma

Source: G-BA resolutions on routine practice data collection

Table 2: Common reasons for terminating data collection procedures include pharmaceutical company opt-out and the limited feasibility of patient recruitment in actual practice.

fit assessment, particularly in non-oncological indications. In addition, a considerable number of orphan drugs are approved based on single-arm studies in therapeutic areas with very small patient populations, where data collection is not methodologically feasible.

Quality deficits in the submitted RCTs may result in the inability to quantify the additional benefit. In many cases, however, no advantage is observed in the patient-relevant endpoints accepted by the G-BA. During the candidate selection process, it is not possible to conduct a comprehensive methodological or substantive review of the available studies in advance; this is the responsibility of the subsequent benefit assessment. Closing existing evidence gaps after approval with an routine practice data collection is generally associated with high hurdles. In many cases, it is no longer feasible to generate the necessary comparative evidence for quantifying additional benefit within a practical timeframe and with reasonable effort, especially for orphan drugs after they have entered the market. Overall, the data collection process is complex and resource-intensive, not only for the G-BA, registry operators, and authorised providers, but also for IQWiG.

Given the small number of suitable candidates, the potential for cost savings through downstream data collection is marginal in comparison to the AMNOG procedure as a whole. Moreover, in view of the rapid innovation cycles in the pharmaceutical industry and the long procedural timelines, the generation of insights relevant to real-world care often appears doubtful.

Outlook and recommendations

Randomised controlled trials (RCTs) will remain the gold standard for both marketing authorisation and benefit assessment.[19] In the context of rare diseases, RCTs may even offer advantages, as the required sample size may be smaller than for routine practice data collection due to the absence of a need for confounder adjustment Moreover, considering IQWiG's methodological requirements, RCTs are the more appropriate instrument when only small to moderate effect sizes are expected.

The primary objective should therefore be to conduct RCTs and to improve the quality of planned RCTs so that they can be used not only for authorisation purposes, but also in national benefit assessments and the EU HTA procedures. If RCTs are not feasible, it is advisable to prospectively collect comparative data on the natural course of disease or on the existing standard of care in parallel with the authorisation study, so that such data can already be submitted for benefit assessment. Established registries should be specifically adapted and used for this purpose.

According to the EMA, statistical models and tests that compare data from single-arm studies with external controls are not sufficient to demonstrate efficacy, as neither modelling techniques nor matching approaches can adequately mitigate bias. As a result, external data from registries may only be used as supportive evidence.18,19 Current authorisation procedures therefore do not provide sufficient incentive to proactively generate suitable data for adjusted indirect comparisons, even in the exceptional cases where single-arm studies are accepted for benefit-risk assessments.

Orphan drugs are already included in the first implementation phase of the EU HTA process, provided they are either oncological products or advanced therapy medicinal products (ATMPs).[20] The EU HTA process is, by design, a comparative evaluation. During the scoping process, a full PICO (population, intervention, comparator, outcome) framework, including a comparator, is defined even for orphan drugs.[21] This raises the question of whether the approach to orphan drugs in the subsequent national AM-

NOG process should be reconsidered.

In the interest of harmonising procedures, it would be consistent to conduct transparent benefit assessments for all pharmaceuticals with new active substances, regardless of their orphan drug status, by comparing them against an appropriate comparator therapy. Likewise, it would be consistent to account for missing evidence in the case of orphan drugs by applying a reduced reimbursement amount early on, as the routine practice data collection procedure, conceived as a corrective mechanism to the statutory assumption of additional benefit, has proven impractical. Incentives for timely market entry remain valuable and could be incorporated into the reimbursement agreements under Section 130b SGB V. These incentives, however, should specifically target orphan drugs that address high medical need or face particular challenges in evidence generation due to extremely small patient populations. In contrast, the routine practice data collection procedure should be phased out, as the legislative goals originally associated with it cannot be achieved in practice. It neither enables system-relevant cost savings, nor does it provide a timely or comprehensive means of addressing the insufficient evidence base at the time of orphan drug authorisation. Instead, the methodological insights and practical experience gained from data collection so far should be used to optimise the planning of studies for future authorisation and HTA procedures, and to sustainably improve the quality of registry infrastructure in Germany.

The evaluations presented in this presentation are the basis of the following publication: Jantschak et al. (2025): Das Verfahren der anwendungsbegleitenden Datenerhebung in der frühen Nutzenbewertung (Routine practice data collection in early benefit assessment), in Monitor Versorgungsforschung (04/25), pp. 34-41. Available online at http://doi.org/10.24945/MVF.04.25.1866-0533.2737

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Experience with routine practice data collection in the context of early benefit assessment

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Following the marketing authorisation of pharmaceuticals, the Federal Joint Committee (G-BA) may require the generation of comparative evidence in the form of routine practice data collection. According to legal requirements, this involves indication-specific data collection without randomisation. Patient registries are considered the primary potential data source for this purpose. In addition to cross-registry challenges such as the need for adaptation and difficulties in patient recruitment, methodological challenges arise from the study design itself (non-randomised comparison) and the inherent risk of substantial bias. For this reason, routine practice data collection is only considered the „second-best" option after (registry-based) randomised controlled trials (RCTs).

Background

Unlike in other European countries, newly authorised pharmaceuticals in Germany are reimbursed by statutory health insurance immediately upon market entry, without the need to demonstrate additional benefit or cost-effectiveness. However, the Act on the Reform of the Market for Medicinal Products (AMNOG)[1] introduced in 2011 requires that all pharmaceuticals with new active substances undergo an early benefit assessment immediately after market entry. This assessment compares the new product against the existing standard therapy in the respective therapeutic area.

For this purpose, robust comparative evidence is required, ideally from randomised controlled trials (RCTs). However, such data is often lacking. Abrams et al.[2] note that although RCTs are considered the gold standard, a large share of authorisation procedures worldwide continues to rely on non-randomised data. According to their analysis, 77% of available advanced therapy pharmaceuticals (ATMPs) in Europe were approved based on non-RCTs, and approximately 54% of ongoing studies in the field of gene therapy are also non-RCTs. These figures are similar in the United States. As a result, adequate comparative data to answer the key questions of early benefit assessment is often unavailable.

A commonly cited argument is that (randomised) comparative studies are not feasible in the context of personalised medicine. However, even highly individualised therapies can be investigated within comparative study frameworks based on treatment strategies. One example is RCTs conducted with chimeric antigen receptor (CAR) T-cell therapies, which are manufactured individually from a patient's T cells and directed specifically against their tumour cells, e.g. axicabtagene ciloleucel.[3]

In addition, post-authorisation requirements imposed by regulatory authorities do not typically generate comparative data that is relevant for benefit assessment. For example, data collection concepts were developed for 15 pharmaceuticals (19 indications) in the context of routine practice data collection. In none of these cases did regulatory authorities mandate studies capable of producing comparative conclusions.

Framework for application-related data collection

To address evidence gaps following marketing authorisation, the instrument of routine practice data collection was introduced in 2019. This instrument authorises the Federal Joint Committee (G-BA) to require pharmaceutical companies to submit routine practice data and analyses for the purpose of benefit assessment (Section 35a (3b) of Book V of the German Social Code – SGB V). Currently, it is the only mechanism available to the G-BA for requesting comparative evidence after authorisation. It is explicitly limited to orphan drugs, pharmaceuticals with conditional marketing authorisation, and those approved under exceptional circumstances. The G-BA may mandate indication-specific data collection without randomisation. Moreover, it may restrict prescribing rights so that only healthcare providers


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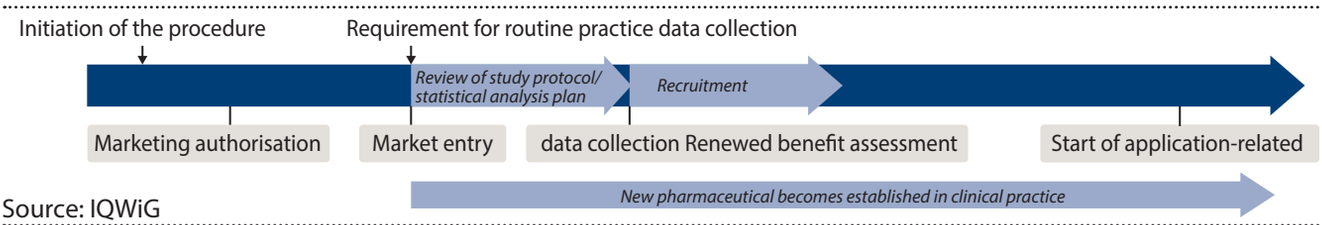
Procedure for routine practice data collection



Source: IQWiG

Figure 1: At present, routine practice data collection is the only option for the Federal Joint Committee (G-BA) to request comparative evidence after the approval of pharmaceuticals.

participating in the data collection are authorised to prescribe the respective pharmaceutical. The procedural timeline is shown in figure 1. While the procedure can be initiated before authorisation, routine practice data collection can be formally mandated no earlier than the point of market entry.

Once the procedure is initiated, the pharmaceutical company is required to submit a study protocol and a statistical analysis plan. These documents are subject to review. If all requirements for data collection are met, the routine practice data collection begins. Following the completion of data collection, a renewed benefit assessment is carried out based on a dossier, followed by price negotiations, whereby price reductions may be possible under certain circumstances. This also applies in cases where, for example, no data collection has been conducted.

The requirements for data collection in the context of routine practice data collection are described in detail in Rapid Report A19-43.[4] Data must be collected for both the new therapy under evaluation and the existing standard of care. In addition to routinely collected data in clinical practice, extensions may be needed, for example to capture health-related quality of life. The collected data must enable conclusions about healthcare provision in Germany, based on sufficiently valid and structured datasets. Alongside study-specific data collection, patient registries are considered the primary potential data sources.

Experience to date with routine practice data collection concept

Experience gained from the routine practice data collection concepts commissioned by the G-BA to date has shown that existing indication-specific registries are generally suitable as a primary data source. In many cases, extensive documentation is available (including protocols and data plans), some of which is publicly accessible. These registries often contain comprehensive datasets, sometimes with precise definitions and/or date specifications. Training on data entry, plausibility checks, and – in some cases – source data verification is also conducted.

In most cases, it is also possible to define the patient population relevant for benefit assessment. However, a number of recurring adjustments have been identified across registries: the need to introduce standardised reporting and data collection time points at sufficient intervals, as well as the standardised collection of adverse events and patient-reported outcomes. In addition, the systematic collection of identified confounders is of critical importance.

However, not all registries identified within the application-related data collection procedures were suitable. A negative example is the IPIG registry for paroxysmal nocturnal haemoglobinuria, where data from individual manufacturers are stored in isolated, separate silos and comparative analysis across these silos is not possible due to contractual restrictions. Despite the extensive data collected, the registry cannot be used for application-related data collection, rendering its data worthless for (additional) benefit assessment.[5]

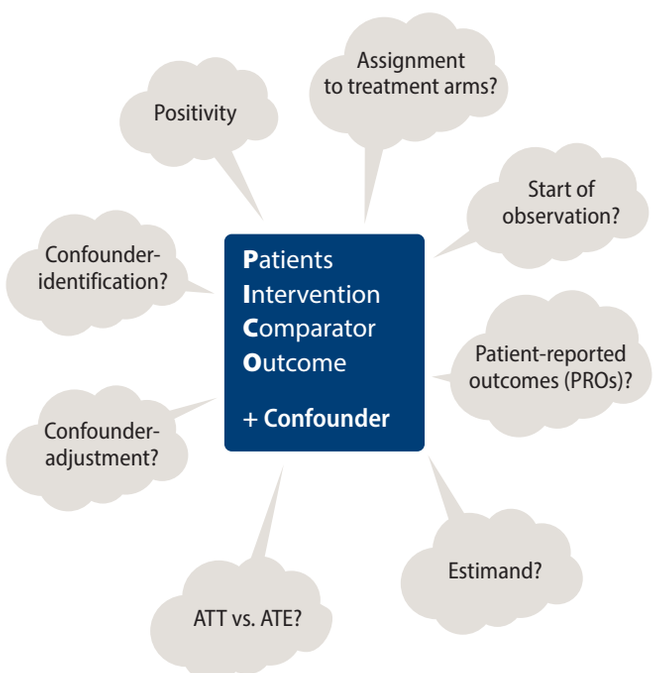
At the start of routine practice data collection, both the new pharmaceutical and the comparator therapy are available in routine care. A particular challenge in designing such data collection arises when a strong preference for the new pharmaceutical is foreseeable, making it questionable whether sufficient recruitment for the comparator arm will be possible in the context of prospective data collection. An example of this is brexucabtagene autoleucel in mantle cell lymphoma.[6] In such cases, it may be necessary to involve treatment centres outside Germany However, it must be ensured that the data remains transferable to the German healthcare context.

Methodological challenges in non-randomised comparative studies

In addition to registries and patient recruitment, further methodological aspects play a significant role in the planning of non-randomised comparative studies; these are illustrated in figure 2. The following section addresses several of these methodological considerations.

Of vital importance is the appropriate definition of the start of observation. This must be uniform across the treatment arms being compared in order to avoid bias in the observed effects, for example due to immortal time bias. Immortal time bias may occur when, as a result of the study design, there is a period during which an event (e.g. death) cannot occur.[7,8] This problem arises, for instance, when the start of observation is set at the time eligibility criteria are met but prior to treatment assignment. As a consequence, treatment assignment is then based on information obtained during follow-up.[9] To prevent this, the temporal components of the study design must be aligned

Selection of methodological aspects in planning a non-randomised comparative study



Source: IQWiG

Figure 2: Numerous methodological aspects must be considered when planning a non-randomised comparative study.

with the start of observation (figure 3).[10]

In the simplest scenario, patients have an indication for treatment switching, resulting in a change either to the intervention or to the comparator therapy Ideally, the start of observation should be defined as the time of the treatment decision (e.g. in a tumour board). Where this is not possible, the closest possible approximation to this time point must be identified. The situation becomes more complex when patients in the comparator arm do not initiate a new therapy but continue to receive the standard treatment.

In such cases, the appropriate definition of the start of observation for patients in the comparator arm is challenging. However, as described above, a uniform start of observation for patients in both arms is essential. Various approaches may be used to estimate the start time, such as the prevalent new-user design.[11]

Another important aspect concerns the collection of patient-reported outcomes in registries. In particular, when comparing different therapeutic approaches (e.g. CAR T-cell therapy versus chemotherapy, one-time gene therapy versus continuous treatment), and when data collection is linked exclusively to clinical visits, differences in the frequency and timing of data collection may arise. This can complicate the interpretation of results, such that registry-based collection alone may not be appropriate. One possible solution is to collect patient-reported outcomes outside the registry using uniform frequency and timing. To facilitate data collection for patients, the use of digital solutions is recommended. Additional relevant methodological aspects are addressed in IQWiG Rapid Report A25-13.[12]

According to the legal framework, routine practice data collection constitutes indication-specific data collection without randomisation. Due to the lack of randomisation, structural equivalence between treatment groups cannot be assumed. As a result, findings from non-randomised comparisons are subject to bias from confounding factors unless appropriate statistical adjustment methods are applied. This requires that all relevant confounders are known and collected in the registry used for the study.

Limiting the analysis to confounders already collected in

Alignment of temporal components of the study design with the start of observation

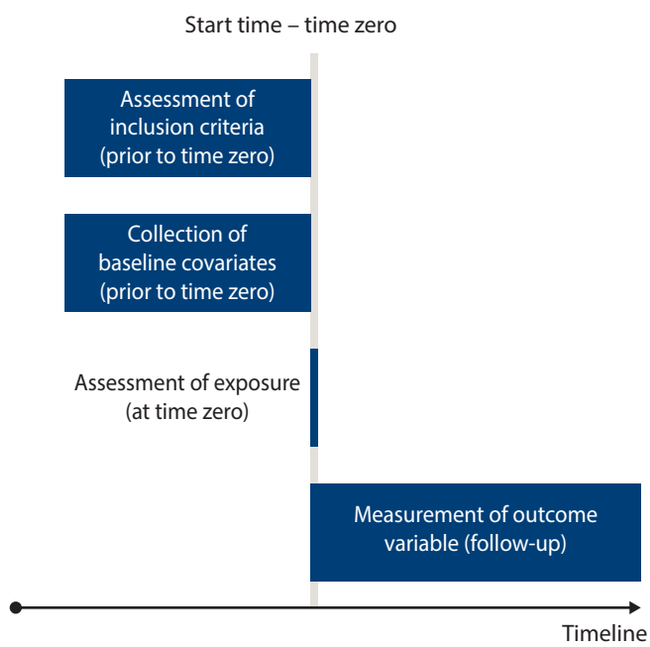


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Figure 3: The start of observation must be consistent across the treatment arms to avoid bias in the observed effects.

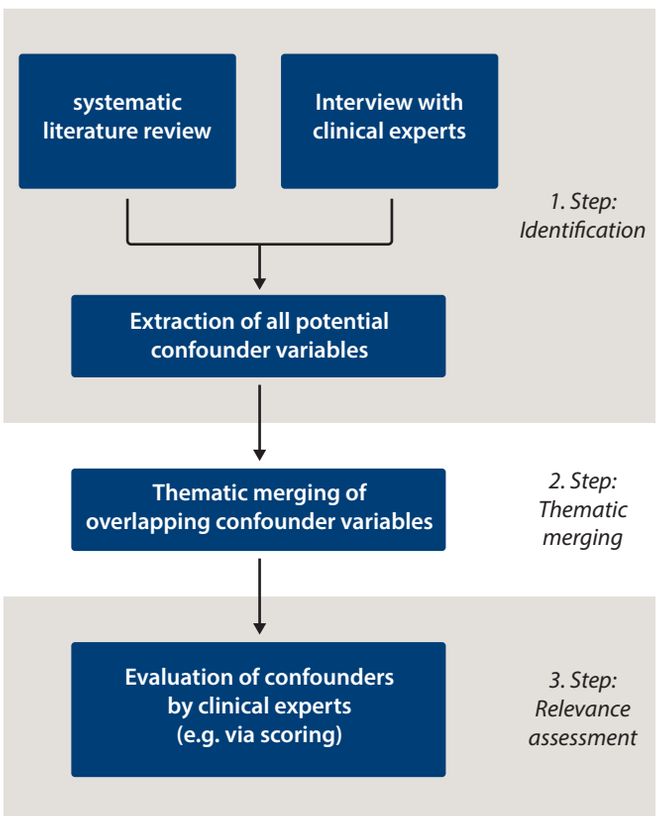
the data source is not sufficient. Relevant confounders must instead be systematically identified a priori. An initial proposal for systematic confounder identification was described by Pufulete et al.[13] Their approach consists of three components: first, a systematic literature review (RCTs and cohort studies); second, structured interviews with clinicians; and third, a survey of clinicians to identify the five most important confounders. This approach has also been recommended for routine practice data collection.

Experience from implementing this approach in study protocols for routine practice data collection to date has shown that the search was often limited to secondary literature (systematic reviews) and that identified factors were sometimes excluded without sufficient justification. Inadequate reasons for exclusion included, for example, „factor is part of the inclusion criteria" or „considered as a subgroup characteristic." Based on these experiences, as well as on confounder identification conducted by IQWiG with the involvement of external experts in the indication of relapsing–remitting multiple sclerosis, a three-step procedure was proposed and documented in the IQWiG working paper GA23-02.[14] The fundamental steps are illustrated in figure 4. In contrast to the methodology described by Pufulete (2022), the approach includes, following a systematic literature review and interviews with clinical experts, a second step aimed at reducing workload by consolidating semantically overlapping confounder variables. This is followed by an assessment of the relevance of the identified confounders. In addition, detailed and transparent documentation of both the process and the results is required. The above-mentioned working paper includes a proposed checklist for manufacturers to support this process.

Limitations of non-randomised comparative studies

Even with the most rigorous analysis and adherence to all stated quality requirements, the inherent risk of substantial bias remains due to the study design (non-randomised comparison). This includes potential deviations in the start of observation or the presence of unknown and unmeasurable confounders. Therefore, a conclusion regarding the

Proposed 3-step procedure for systematic confounder identification



Source: IQWiG

Figure 4: A three-step approach is proposed for the systematic identification of relevant confounders.

Shifted null hypothesis

Source: IQWiG

Figure 5: The interpretation of results must take into account the potential bias due to the non-randomised comparison. This is done by means of a shifted null hypothesis.

benefit or harm of an intervention is only meaningful above a certain effect size. Otherwise, it cannot be ruled out that the observed effect is not due to the intervention itself but rather the result of bias.

Interpretation of the results must thus consider potential distortions inherent to the non-randomised comparison. Within the framework of routine practice data collection, this is addressed by means of a shifted null hypothesis. Accordingly, an additional benefit can only be inferred if the observed effect, including its confidence interval, lies beyond the defined threshold (test of a shifted null hypothesis, figure 5). The actual threshold for initiating an routine practice data collection is determined by the specific quality of the available data.

Conclusions and outlook

Routine practice data collections aim to close existing evidence gaps but, according to legal requirements, must be conducted without randomisation. This results in increased demands on the scope of data collection, particularly due to the need to gather data on relevant confounders. Moreover, a larger sample size is usually required, not least because of the necessary statistical adjustment for these confounders. As a result, the effort required for a comparative, real-world study with randomisation is generally lower than for a study without randomisation since the collection and adjustment for confounders may be omitted. For this reason, an routine practice data collection is only the „second-best" solution after (registry-based) randomised controlled trials (RCTs). Such (registry-based) RCTs are also feasible for interventions targeting small populations, such as orphan drugs or advanced therapy pharmaceuticals (ATMPs), provided that they are conducted in a timely manner (i.e. before marketing authorisation).

In exceptional cases where it is not possible to conduct an RCT, a prospective data collection for the comparator therapy should be initiated in a registry, ideally at the same time as the single-arm pivotal trial based on a shared study protocol. This study protocol should also define the confounders identified in advance, which must be collected for all patients, so that the comparative analysis can yield meaningful results.

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Theses on the further development of the EU HTA methodology

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Health Technology Assessment (HTA) is undergoing a transformation within the European Union (EU) and is facing major challenges. Since 2025, applications for the reimbursement of oncological pharmaceuticals have been centrally evaluated within the framework of Joint Clinical Assessments (JCA) by EU HTA. An additional challenge lies in the increasing number of marketing authorisations granted by the European Medicines Agency (EMA) for oncological pharmaceuticals based on single-arm studies without a control group. As a result, HTA applications increasingly rely on indirect comparisons using external controls, which are predominantly rejected by key decision-makers such as the Federal Joint Committee (G-BA) due to methodological issues (lack of RCTs) and an insufficient demonstration of additional benefit. This article presents seven theses that outline the fundamental methodological problems of HTA in Europe and provides suggestions for the necessary further development of HTA methodology, particularly with regard to indirect comparisons.

HTA is undergoing a transformation in the EU. Since early 2025, Joint Clinical Assessments (JCA) apply to reimbursement applications for new oncological pharmaceuticals. Appraisals and potential reimbursement decisions are then conducted at the member state level. Regulatory authorities in the USA (FDA) and EMA are granting an increasing number of approvals for orphan and non-orphan pharmaceuticals via accelerated procedures. Furthermore, approvals of single-arm studies without a control arm by the FDA and EMA are on the rise, with these trends being more pronounced in the USA than in the EU.[1] These developments necessarily lead to the use of indirect comparisons with external controls in HTAs.

EU HTA has published methodological guidelines on indirect comparison procedures as well as guidance for submissions under the new rules.[2,3]

The fundamental challenges of HTAs for oncological pharmaceuticals that are not based on randomised evidence and do not meet the requirements of HTA organisations for demonstrating additional benefit have been exacerbated by these developments. These challenges often include a lack of observational data from registries or studies of sufficient quality, as well as methodological weaknesses in data analysis.

Moreover, leading decision-makers in the EU, such as the G-BA, predominantly issue negative assessments for applications based on evidence from indirect comparisons using external controls.[4,5] This article outlines seven theses that address the fundamental methodological and procedural issues of EU HTA.

Solving these issues is a prerequisite for more efficient, tailored HTA processes that offer applicants clearer guidance for submissions based on limited evidence using external controls. This is also important for patients with limited

treatment options, to ensure timely access to new therapies for these groups.

Thesis 1: Uncertainty in assessing additional benefit in HTAs and the opportunity costs of limiting decision uncertainty must be kept in defined balance

Regulatory authorities conduct benefit-risk assessments based on the totality of available evidence, which includes the treatment context, evidence on benefits and risks, data uncertainty, and options for risk minimisation and risk management.[6] In contrast, HTA organisations focus on decision uncertainty concerning the effectiveness and safety of a novel technology or intervention compared to current clinical practice (comparator therapy), as well as on the financial and healthcare system implications of reimbursement.[7,8]

The current trend towards more single-arm approval studies without active control arms increases decision uncertainty for HTA organisations since comparator standards are based on (often historical) observational data and are susceptible to bias. The demand for data from experimental studies or high-quality, prospectively collected observational data on long-term effectiveness and safety of new pharmaceuticals must consider the associated opportunity costs in the decision-making or consultation process, for example, within the framework of a Joint Scientific Consultation (JSC).

Early reimbursement of a pharmaceutical with an uncertain evidence base may address the need for new treatment options, particularly for patients with limited alternatives, at the potential „cost" of approving a pharmaceutical that may later prove to offer no additional benefit or may reveal serious, previously unknown side effects (type I error). In this scenario, patients are exposed to unnecessary or even harmful treatments, and healthcare systems, social insurers, and premium payers incur additional costs without corresponding benefits. Conversely, delaying reimbursement of a pharmaceutical that appears promising based on early clinical data and surrogate endpoints – until high-quality (experimental) evidence becomes available – may deny patients with limited options timely access to a superior therapy and worsen their prognosis. Furthermore, this can result in significant additional costs for applicants, which could lead to increased prices for therapies with demonstrated benefit (type II error).

Decision uncertainty can be reduced by several means. Methodological shortcomings in applications based on observational data can be mitigated using newer approa-

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Emeritus Professor of Clinical Epidemiology, University of Basel; Consultant, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel (2001-2021); Lecturer, Department of Health Sciences and Technology, ETH Zurich (2017-2021) He held research fellowships at the University of California, Berkeley (USA), McMaster University in Hamilton (Canada), and Stanford University in Palo Alto (USA). The method for indirect comparisons developed by Professor Bucher has been widely adopted in HTA laid the foundation for the development of network meta-analysis techniques.

Contextualisation of the Process for Evidence-Based Data Collection for HTA

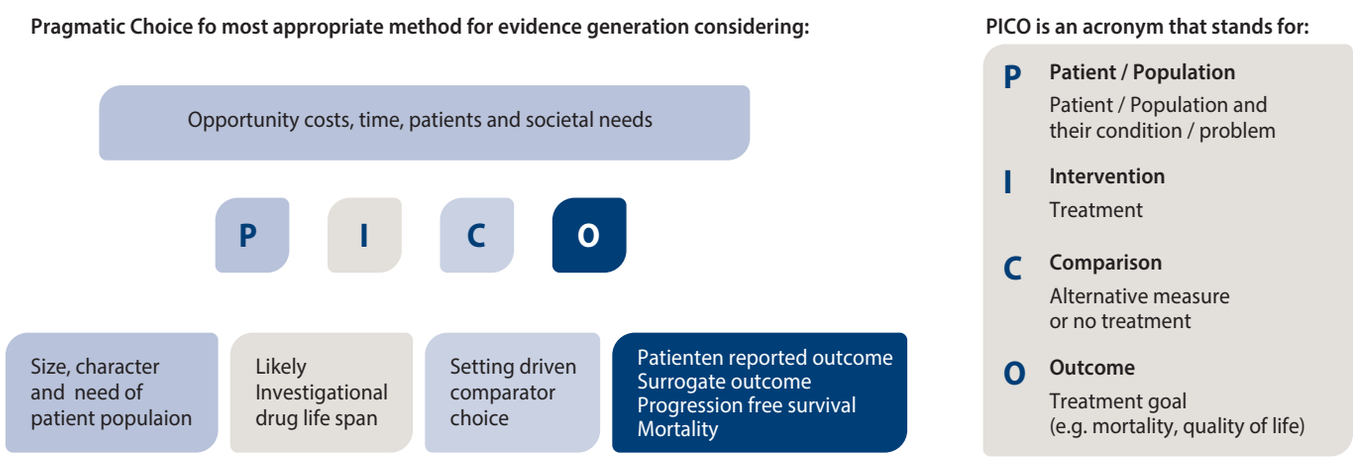

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Figure 1: Consideration must be given to opportunity costs, the expected time frame, and the potential benefits for both patients and society.

ches (outlined below). Conditional pricing and value-based pricing models can reduce the financial risk for payers when reimbursing pharmaceuticals with limited evidence of benefit. Conditional data collection for early benefit assessments is another way to limit decision uncertainty. However, a review found that between 2019 and 2024, the G-BA implemented the conditional data collection for orphan pharmaceuticals in only five cases, with additional benefit rarely demonstrated, and the data collection process was complex and time-consuming.[9]

Thesis 2: HTA is always context-specific and must place greater focus on processes of evidence-based data generation

In a dynamic and competitive environment with rapidly evolving new therapeutic approaches, decisions on the optimal methodological approaches for addressing a PICO question for a new pharmaceutical must be made in a pragmatic manner. In this process, opportunity costs, the expected time frame of use of a pharmaceutical, as well as the benefit for patients and society must also be taken into account (figure 1).

The context-specific nature of HTA is readily apparent from the disease condition, its prevalence, and the size and needs of the patient population (the „P" in PICO). HTA organisations in individual Member States (MS) may, for example, in the context of scoping, require restriction of the patient population to subgroups defined by specific prognostic disease characteristics. This can have far-reaching consequences for the planning and achievement of the necessary patient numbers. Less attention, however, is paid to contextual factors relating to the intervention un-

der investigation (the „I" in PICO), such as the duration of response to an intervention or the expected time window for clinical use in treating a serious progressive condition. One example illustrates the issue.

Antiviral pharmaceuticals used as pre-exposure prophylaxis against COVID-19 are important for patients with immunodeficiency caused either by an underlying disease or by immunosuppressive therapy. The anti-spike monoclonal antibody sipavibart was investigated by the applicant for its neutralisation potency against SARS-CoV-2 and for the prevention of COVID-19 infections in a randomised controlled trial (RCT) involving immunocompromised individuals,[10] which also served as the basis for the AMNOG application. The study excluded infections with specific virus variants against which the substance had no effect.

During the recruitment phase, over one third of patients with symptomatic infection were already infected with a resistant variant. As a result, neutralisation evaluations had to draw on external historical controls in the context of so-called immunobridging procedures. By the time the application was submitted, epidemiological studies showed that over 90 per cent of symptomatic infections in the general population were caused by the variant in question, against which the substance had no efficacy.

The rapid evolution of the virus thus made it impossible to assess the effectiveness of the antibody in the context of an RCT. In conditions involving rapid pathophysiological evolution that limits a pharmaceutical's susceptibility profile (drug susceptibility or drug resistance), the RCT may not represent the ideal design for demonstrating effectiveness.

The context-specific nature of HTA becomes especially apparent in the case of JCAs when it comes to the choice of comparator therapy (the „C" in PICO, comparator). The choice of comparator should be based on clinical criteria and represent „the best available alternative treatment". However, the availability, type, and use of comparator therapies may vary across MS and may involve one or more treatment options considered „equivalent". This issue can be addressed either by refining the PICO to restrict it to certain patient subgroups, or by expanding the PICOs to include additional comparator strategies. Both approaches are problematic in terms of increased effort, questions regarding the feasibility of additional comparisons, and a rising risk of type I error due to multiple comparisons.

Context also plays a significant role in the choice of endpoint (the „O" in PICO, outcome). For many applications, particularly for oncological pharmaceuticals and pharmaceuticals for rare diseases, endpoints such as overall survival, as favoured by IQWiG, are often not feasible. Progression-free survival is a meaningful surrogate endpoint from the patient perspective; it can be well documented in early phase II to III studies and is accepted by regulatory authorities. Patient-reported outcomes (PROs) are still not sufficiently taken into account in the planning phase of early clinical studies, although they are highly relevant from the patient perspective.

The contextuality of HTA, which is accentuated by cross-MS JCAs, requires improved and early communication and coordination between the applicant, regulatory authorities, and HTA organisations. Maximum attention must be paid to coordinated study planning and data generation in phase II to III marketing authorisation studies and any additional real-world evidence (RWE) collection via registries.

This requires improved collaboration between the clinicians involved from centres of excellence and networks with high patient recruitment potential, and the pharmaceutical industry. This in turn calls for newly designed incentive models that create win-win situations for all stakeholders. Models that leave data ownership with the clinics and networks should be preferred, as they simultaneously

strengthen independent academic research and pose fewer conflicts concerning data protection.

Thesis 3: HTA must be based on a systematic and comprehensive search for and inclusion of all methods for comparative effectiveness analysis

Current EU HTA guidelines on indirect comparisons place their emphasis on meta-analytic comparison methods, particularly those based on aggregated data from RCTs.[2,3] A systematic search for and description of methods for analysing observational data (an increasingly important component of evidence generation) is lacking. Techniques such as causal models or target trial emulation, the definition of estimands,[11] quantitative bias analysis,[12] or the application of Bayesian approaches to the analysis of observational data,[13] methods that have been used for many years in various clinical research domains, are not currently included in the EU HTA guidelines.

It is indicative that countries with a strong academic culture in clinical epidemiology and biostatistics, such as the Netherlands, the UK, Canada, and Australia, are earlier and more proactive in incorporating newer research methods into their HTA guidelines than, for instance, Germany or France. Closer collaboration between academic centres with relevant expertise and HTA organisations, especially with the HTA Coordination Group (HTACG), to develop more evidence-based methodological guidelines on comparative effectiveness is both desirable and urgently needed.

Thesis 4: HTA requires a transparent and evidence-based presentation and weighting of comparative effectiveness methods

The current EU HTA guidelines lack a clear, structured overview of the available methodological approaches to comparative effectiveness. What is missing is a systematic evaluation of the strengths and limitations of different methods, along with guidance on when, based on the available data, a particular method involving external controls may be considered an appropriate way to address a given PICO question. Such orientation would be of considerable practical value for applicants.

In 2024, EU HTA published its first set of recommendations and guidelines on how to assess risk of bias in observational studies. It remains to be seen to what extent these will be reflected in future JCAs.[14] One tool that has long been established in this area is ROBINS-I, which has been in use for the past ten years. It provides a framework for assessing risk of bias in intervention studies based on observational data.[15]

ROBINS-I is built around the concept of emulating a hypothetical pragmatic randomised trial and covers seven domains of bias: those occurring before the intervention (e.g. confounding, selection bias), during the intervention (e.g. differential and non-differential misclassification), and after the intervention (e.g. deviations from intended treatment, missing data, endpoint misclassification, and selective reporting). The tool can be integrated into GRADE, the globally recognised system for rating the quality of evidence.[16] While GRADE has traditionally focused on randomised controlled trials, integrating ROBINS-I allows for the structured comparison of evidence from both randomised and non-randomised studies within a unified system.

Selective reporting bias can also be mitigated by strict adherence to established reporting standards such as STROBE for observational studies.[17] However, both HTA organisations and applicants have so far paid too little attention to this.

GRADE also offers a framework for managing uncertainty in evidence interpretation. It identifies factors that can strengthen or weaken our confidence in the reliability of

the evidence base.[18] In addition, the Evidence to Decision (EtD) framework developed by GRADE is a transparent system that enables decision-makers to request evidence, interpret it systematically, and formulate decisions in a transparent manner.[19] The framework supports decision-makers and patient organisations who are responsible for implementing recommendations or are directly affected by them. This ensures transparency not only in the assessment criteria themselves, but also in the underlying evidence on which they are based. The evaluation system also helps decision-makers determine whether, and in what form, the available evidence can be transferred to their own healthcare system, implemented as is, or adapted where necessary.

The GRADE system for evaluating evidence, along with its decision-making and implementation framework, should be considered in the further development of JCAs and examined for its potential to be adapted and applied in HTA.

Thesis 5: Duplication between EU HTA and national HTA bodies must be reduced

To ensure that JCAs lead to meaningful synergies, the methodological approaches used by EU HTA must be presented in a way that allows all HTA bodies in the Member States to understand and adopt them. A more systematic presentation of methodology, particularly for HTA reports based on external controls, along with full transparency in how both methodology and evidence are described and evaluated, is essential to avoid unnecessary duplication between JCAs and national assessor teams. One key area of divergence between JCAs and the expectations of HTA bodies in the Member States is the choice of comparator therapy. Involving all relevant national HTA stakeholders early in the process, ideally through Joint Scientific Consultations, can help streamline and focus the scope of assessments, ensuring that the number of PICOs remains both manageable and meaningful.

Thesis 6: Assessments and appraisals of modern technologies must be strictly separated in JCAs

Assessment and appraisal of additional benefit are the two core components for determining the value of modern technologies and for making reimbursement decisions on new medical interventions. However, how assessment and appraisal are handled varies between Member States and is often not clearly defined. With assessments now being centralised at the European level, while appraisal of the evidence remains the responsibility of individual countries, a strict separation between assessment and appraisal is essential.[20]

Reimbursement decisions for new pharmaceuticals, especially those with early marketing authorisation and limited data on efficacy and additional benefit, are often made under conditions of uncertainty. As a first step, the appraisal process must determine the extent to which the assessment allows for a reliable evidence base. Evaluation of the certainty of evidence, internal validity, and robustness of the HTA report should be based on common EU-wide criteria. Nevertheless, in individual Member States, factors such as access considerations, innovative potential, or investment capacity can complicate the determination of additional benefit. Willingness or ability to bear such risks may in turn determined by other factors, such as the disease's relevance within the national context, expected budget impact, or the need to prioritise investments for other, more pressing health issues. These aspects must be addressed in a second step.[20]

While the foundations of the appraisal process do not formally fall within the remit of the JCA, harmonising ap-

praisal procedures and criteria within the Member States, and thereby reducing duplication, should nonetheless be pursued.[20] This will require additional financial and personnel resources to support the transfer of know-how. The autonomy of Member States in making reimbursement decisions remains unaffected by such alignment of appraisal frameworks. However, it would lead to greater transparency in national appraisal processes and reimbursement decisions for stakeholders such as patient organisations and applicants.[20]

Thesis 7: Joint Scientific Consultations (JSCs) require closer alignment between EMA and EU HTA

Joint Scientific Consultations are intended to enable early dialogue between applicants and HTA organisations on the clinical development programme of a new substance, prior to the submission of a study protocol for regulatory approval. These consultations can and should be coordinated in parallel with scientific advice from the EMA to align timelines and dossier submission. The aim of JSCs is to streamline and synchronise regulatory and HTA processes in order to generate a robust evidence base that supports sound decision-making for both marketing authorisation and reimbursement. JSCs are especially relevant in therapeutic areas with high unmet need and significant data uncertainty.

In the first year under the new EU framework, the HTA Coordination Group (HTACG) allocated only a limited number of 5 to 7 slots for JSCs on medicinal products in order to allow Member States to build up capacity. Eligibility criteria for these limited slots include that study protocols for regulatory approval are still in the planning stage. Further selection criteria include high unmet need, first-in-class status, expected impact on public health and healthcare systems, cross-country relevance within the EU, anticipated additional benefit at European level, and alignment with EU-wide clinical research priorities. The JSC process is expected to take four to five months. Applicants must weigh the benefits and risks of pursuing a JSC, including questions of timing, availability, likelihood of selection, and budget. It should also be noted that JSC reports and protocols must be submitted along with the JCA dossier. If substantial deviations arise between the scientific advice provided during the JSC and the actual content of the JCA, such as in the final choice of comparator, this may raise questions of legitimacy and negatively affect reimbursement decisions.

JSCs offer significant opportunities for synergy, particularly when involving both EMA and EU HTA, and especially in applications where randomised controlled trials (RCTs) are not feasible. Issues such as the use of external controls from cohort studies or registries can be clarified at an early stage. Planning a phase II study with early incorporation of prospectively collected comparator data can help assess the feasibility of a target trial emulation. Other topics, such as the definition of a minimal dataset with key confounding variables, or handling deviations from the treatment protocol (e.g. due to disease progression or potential intolerances), can help strengthen submissions and improve the demonstration of additional benefit in HTA.

A recently published joint position paper by the EMA and the Heads of HTA Agencies Group acknowledges the importance of real-world evidence from prospectively collected registries and cohort studies, while also reaffirming the primacy of RCTs as the gold standard of evidence.[21] However, the paper does not discuss causal models or target trial emulation. Instead, it highlights the potential of pragmatic trials, platform trials[22], and trials nested within cohort studies (Trials within Cohorts, or TwiCs), especially for oncology.

Yet, a review found that by 2023, only 145 platform trials had been planned or conducted, mostly in oncology and COVID-19.[23] Many platform trials use Bayesian designs that allow probabilities to be specified for benefit, lack of benefit, or harm; others use response-adaptive randomisation. These approaches are methodologically demanding and remain relatively uncommon. Following the pandemic, the use of platform trials declined significantly. Although TwiCs were first introduced 20 years ago[24], their validity strongly depends on the quality of the underlying cohort studies. Only a few academic centres currently have the capacity to run high-quality cohort studies and apply these advanced designs effectively.

Another review found that between 2005 and 2022, just 45 TwiCs had been conducted, primarily by a handful of academic centres and mainly in oncology and infectious diseases.[25] Our group was among the first to embed a platform trial within the Swiss HIV Cohort and the Swiss Transplant Cohort to assess the immunological efficacy and safety of the first two authorised COVID-19 vaccines in immunodeficient patients.[26,27] The design proved highly advantageous for rapid patient recruitment, although the effort required to plan and establish the platform was substantial. While such „newer" study designs are undoubtedly promising and should see wider adoption, they remain methodologically complex and require high-quality, prospectively collected registry and cohort data. They are no panacea, and certainly not a substitute for a necessary and overdue discussion among HTA decision-makers and methodologists on the role of comparative effectiveness methods not yet well established in HTA, such as target trial emulation and causal models.

A fundamental limitation of the current JSC process is the lack of explicit and transparent description of contextual factors and decision-making processes under uncertainty on the part of both regulators and HTA bodies.[8] A harmonisation of the parallel consultation process between the EMA and EU HTA only constitutes progress if it genuinely creates synergies, saves resources, and, in particular, leads to a gain in time.

At its core, the success of JSCs depends on making the contextual differences in how uncertainty is understood, and classified, by regulators and HTA organisations fully explicit. Harmonisation between regulatory and HTA processes can only work if the distinct taxonomies and perspectives on uncertainty that shape EMA and HTA decision-making are acknowledged and addressed for all stakeholders involved.[8]

Conclusions

The approval of new pharmaceuticals based solely on single-arm trials requires the development of risk management strategies within HTA to address uncertainty, strategies that make the associated opportunity costs for patients, society, and the healthcare system explicit, and that are communicated transparently during reimbursement decision-making processes. Evidence generation for HTA is a complex and highly context-dependent process. Especially when evaluating novel therapeutic approaches for conditions with limited treatment options, pragmatic methods are increasingly needed, methods that appropriately reflect the specific challenges of evidence generation within the relevant clinical and healthcare context.

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Advanced therapeutic medicinal products for rare diseases: The Italian Perspective

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In the European Union (EU), advanced therapy medicinal products (ATMPs) are granted central licensing by the European Commission based on a positive opinion from the European Medicines Agency (EMA). However, for these products to be freely accessible to the population, they must be reimbursed at the national level. In Italy, the Italian Medicines Agency (AIFA) oversees regulation, health technology assessment (HTA), pricing, and reimbursement of medicinal products for human use, but regional and local authorities are responsible for pharmaceutical prescriptions and usage.

In this context, ATMPs for rare diseases could benefit from a more integrated approach that combines access to innovative treatments with sustainability. For example, ATMPs that are granted orphan designation can be expedited for review by AIFA and qualify for financial incentives. Furthermore, AIFA has implemented an algorithm to assess the additional therapeutic benefits of new treatments in settings where medical needs are unmet. Taken together, this framework has led to a high reimbursement rate for EU-approved Advanced Therapy Medicinal Products (ATMPs). Currently, 79 % of the ATMPs approved in the EU are reimbursed in Italy.

Background

Echoing other countries' approach to boost research and development in rare diseases, the European Union (EU) passed Regulation (EC) 141/2000, establishing a framework of incentives (such as fee waivers, protocol assistance, and a period of 10 years of market exclusivity once the product is marketed) to counterbalance their poor attractiveness under normal market conditions.[1] Meanwhile, the advent of recombinant DNA technologies paved the way for the development of new therapeutic approaches, based on gene, cell, and tissue therapies. On these grounds, Regulation (EC) 1394/2007 established a specific framework for advanced therapy medicinal products (ATMPs), building common rules for their development and authorisation to ensure public health protection while fostering innovation.[2]

In the EU, both orphan medicinal products (OMPs) and ATMPs are licensed at the central level by the European Commission upon the European Medicines Agency's (EMA) scientific evaluation by relevant expert committees. ATMPs may potentially be granted orphan designation when they meet the eligibility criteria, i.e., targeting a life-threatening or debilitating condition that affects no more than 5 in 10,000 people in the EU, and being of significant benefit over existing methods when applicable.[3,4]

These products are also potentially eligible for specific regulatory programs implemented to prioritise medicines for faster access to patients: authorisation under exceptional circumstances (2004) and conditional marketing authorisation (2006) as expedited approval pathways; accelerated assessment (2005) as regulatory review scheme; and the priority medicines scheme (PRIME), launched by the EMA in 2016, which offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accele-

rated assessment of medicines applications.[5]

The convergence of scientific progress and regulatory flexibility has therefore promoted a shift in medicines approval, allowing new therapeutic avenues for patients with serious or life-threatening diseases to be authorised with less robust evidence than in the past. However, the combination of a lower evidence quality with extremely high prices has posed new challenges for health technology assessment (HTA) bodies and payers.[6]

In this paper, we provide an overview of the development, approval, and access to ATMPs for rare diseases by briefly outlining the relevant European regulatory framework and then describing how these technologies are evaluated in Italy, including strategies to speed up the assessment and reimbursement while governing expenditure, as well as their impact on patient access.

The Italian pharmaceutical system

In Italy, the National Health Service (NHS) was founded in 1978 as a Beveridge model, thus providing universal coverage and access to healthcare free of charge to the entire population. Today, it is organised into three levels:

1) **the central government** sets the framework of basic principles by defining the Essential Levels of Assistance (LEAs), which must be assured homogenously to citizens throughout the country. In this context, the Italian Medicines Agency (AIFA) – the national competent authority – governs medicines regulation, pharmaceutical expenditu-

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Steps and criteria for establishing pricing and reimbursement in Italy

1. Marketing Authorisation Holder (MAH) applies for the pricing and reimbursement by submitting a dossier to AIFA.

2. Administrative check to evaluate the completeness of the application

3. AIFA's HTA and Pharmaceutical Economy Division (HTA-PED) and its Secretariat perform a health technology assessment on the therapeutic value and place in therapy of the proposed medicinal product in relation to comparators, its innovativeness, and draft a proposal for the definition of the price with respect to the MAH's request.

4. AIFA's external Scientific and Economic Committee (CSE) evaluates the MAH's proposal as well as the HTA-PED assessment and issues a binding opinion on the therapeutic value of the medicinal product by defining its place in therapy, its supply regime, and the innovation status (if requested by the MAH). Additionally, the CSE proposes a negotiation agreement to the MAH, with the definition of the reimbursement price and the elements of a conditional reimbursement agreement, if necessary (https://www.aifa.gov.it/en/commissione-scientifica-economica) .

5. The MAH receives the CSE's place in therapy definition and pricing request and can either accept the proposal or send a rebuttal letter in which they would make a counteroffer or give further information to inform the CSE's decision on the place in therapy. In the latter case, the HTA-PED and the CSE will evaluate the new data in an iterative process until an agreement is found, and the product is made reimbursable by the NHS and listed in Class A or Class H. If an agreement is not found, the procedure terminates with the non-reimbursable decision of the medicinal product and is listed in Class C, with a freely set price defined by the MAH and monitored by AIFA.

6. The results of the negotiation procedure are submitted to AIFA's management board for ratification of the final decision and subsequent publication of the decision on reimbursement in OIJ.

Of note, the price negotiated by AIFA represents the maximum sale price for the Italian NHS, which means that Regions are entitled to further negotiate it at the regional level with tender procedures.

Source: https://www.aifa.gov.it/en/normativa-di-riferimento-spesa-farmaceutica
https://www.aifa.gov.it/en/regolamento-cse

Box 1: The Italian Medicines Agency (AIFA) governs medicines regulation, pharmaceutical expenditure and is responsible for HTA and pricing and reimbursement.

re and is responsible for HTA and pricing and reimbursement (Box 1); 2) **Regional governments** legislate within their own competencies, define healthcare policies, and are responsible for health service organisation and expenditure. With regards to pharmaceuticals, Regions contribute to respecting the pharmaceutical expenditure ceiling set at the central level (as part of the healthcare expenditure); 3) **the local level** delivers the healthcare to citizens through a network of hospitals, healthcare units, general practitioners and pharmacies.[7]

For these reasons, an interregional variability may characterise not only the whole healthcare organisation but also the uptake of medicines, as some Regions may limit the use of medicines after the publication of AIFA's decision on reimbursement in the Italian Official Journal (OIJ).[8]

The Italian regulatory framework for Orphan and Advanced Therapeutic Medicinal Products

According to Italian legislation, ATMPs do not have a specific regulatory framework beyond the EU one. Access to ATMPs can be fostered when they are granted EU orphan designation and/or recognised as innovative by AIFA, as well as in some special situations.

Pursuant to Italian Law 189/2012, Marketing Authorisation Holder (MAH) of OMPs, medicines for exclusive hospital use, and medicines having exceptional therapeutic relevance are entitled to a fast-track procedure where they can submit the Pricing and Reimbursement (P&R) dossier to AIFA after the Committee for Human Medicinal Products (CHMP) positive opinion, before the European Commission issues the marketing authorisation. Moreover, these products are entitled to a faster reimbursement procedure, to be completed within 100 days from application, instead of the standard 180 days. Law 145/2018 establishes additional national benefits for OMPs, including an exemption from the claw-back that pharmaceutical companies must pay if NHS spending exceeds its programmed cap.[9]

In addition to usual reimbursement pathways, in Italy, patients may benefit from free access to ATMPs for rare diseases before licensing, including the use for indications other than their original approval (off-label use). The routes for early access include: Law 648/1996, which allows for the reimbursement of medicinal products by the National Health Service and AIFA for a specific indication; compassionate use, which involves the manufacturer directly providing the medicine free of charge; non-repetitive use of ATMPs, consists of preparing the medicinal product directly from a cell factory, with the requesting clinical centre covering the associated costs; Law 94/98, allowing for access to a medicinal product that is regularly marketed but used for a different indication from that for which it was authorized.[10,11]

Given their intrinsic technological complexity and targeted areas of unmet medical needs, ATMPs for rare diseases are usually perceived by stakeholders as innovative medicines. However, novelty does not necessarily imply innovation. To close this informative gap, AIFA has implemented a decision-making process for recognising the innovativeness of a new medicine, a status that allows access to specific benefits as well as financial measures concerning the governance of pharmaceutical expenditure. Innovative medicines have access to a dedicated fund, immediate market access in all Regions and are exempt from extra mandatory discounts for 36 months. The innovation status of a medicinal product for a specific indication is assessed based on criteria that have been changing over the years.

From 2017 to 2025, innovativeness was appraised based on three criteria: unmet need, clinical added value, and robustness of clinical evidence. The first two have a five-point score (maximum, important, moderate, poor and ab-

Scoring system of the innovative status of medicinal products in Italy

Therapeutic need	Added therapeutic value	Quality of evidence
Maximum	Maximum	High
Important	Important	
Moderate	Moderate	Moderate
Poor	Poor	Low[a]
Absent	Absent	Very Low
	Not Evaluable	

Light blue cells: the score needed to be awarded the innovative status

[a] Medicinal products indicated for rare and ultra-rare diseases can be awarded innovativeness even with a "Low" quality of evidence.

Source: https://www.aifa.gov.it/en/farmaci-innovativi

Table 1: AIFA has implemented a decision-making process for recognising the innovativeness of a new medicine. Innovative medicines have access to to a dedicated fund and immediate market access in all Regions.

sent), while the third one is a four-point GRADE score (high, moderate, low, and very low).[12] Innovativeness could be awarded as full for products that had at least an important unmet need, important clinical added value and moderate quality of evidence. In the case of moderate unmet need, moderate clinical added value and moderate quality of evidence, there was the possibility to award a conditional innovativeness status, with an 18-month validity, that would only give immediate market access, without economic benefits. An exception was allowed for products indicated for rare diseases, which could be considered innovative even with low quality of evidence.

In 2025, innovativeness appraisal was further revised, and the option to award conditional innovativeness was removed. Additionally, a new eligibility threshold based on prevalence was introduced, allowing only products intended to treat severe conditions with low to medium prevalence to qualify for innovative status.

The criteria for assessing added clinical value now include six possible scores, which allows for the possibility that a product may be classified as „not evaluable" when compared to existing therapeutic alternatives. Under this revised framework, a medicinal product is deemed innovative for a specific indication if it meets at least moderate standards for unmet need, added clinical benefit, and quality of evidence. The exception for rare and ultra-rare disease in case of low evidence quality is maintained (Table 1).[13]

The limited understanding of diseases, combined with the small number of patients available for treatment, creates significant challenges in the clinical development of OMPs, often accompanied by major evidence gaps and uncertainties. This presents the major issue for payers when making reimbursement decisions and determining the added value of these products.

This also includes ATMPs, whose appraisal is made even more complex by skyrocketing prices. Italy is one of the countries where managed entry agreements (MEAs) have been used to harness uncertainty about the number of patients to be treated, as well as uncertainties on the efficacy of treatments. These agreements have enabled access to

Managed Entry Agreements used in Italy

Monitoring registries based on MEAs (Patient-level)	Financial-based	Cost sharing (CS)	A confidential price discount is applied to (initial) treatment cycles for all eligible patients.
		Capping	Definition of a cap on the number of doses or packs per patient that the NHS will pay. Each additional package cost is refunded by the pharmaceutical company.
	Outcome-based	Risk Sharing (RS)	A confidential price discount is applied to treatment cycles for patients who have not responded to treatment.
		Payment by Result (PBR)	Full refund from the pharmaceutical company for patients who have not responded to treatment.
Expenditure and Consumption Monitoring Information Flows (Population-level)	Financial-based	Spending cap	Definition of a spending cap for the product expenditure. In case of expenditure excess, the pharmaceutical company has to pay back the difference to the NHS.
		Price-Volume	Definition of incremental price discounts over time or according to predefined expenditure thresholds.

Source: AIFA on file

Table 2: Managed Entry Agreements (MEA) on patient-level are implemented through AIFA's monitoring registries, whereas opulation-level MEAs are implemented through the expenditure and consumption monitoring information flows.

therapies where traditional appraisal processes would have led to a failure or a prolongation of negotiations.

Two types of MEAs have been used so far, depending on the types of uncertainty faced by the decision-makers: financial-based agreements are generally used in the case of uncertainty on the number of patients, or duration of treatment, while outcome-based agreements are commonly used in the cases of uncertainty on the efficacy of the treatment. Patient-level MEAs are implemented through AIFA's monitoring registries, a national web-based system funded by pharmaceutical companies and governed by AIFA, whereas population-level MEAs are implemented through the expenditure and consumption monitoring information flows (Table 2).[14]

Reimbursement of ATMPs in Italy

Since the entry into force of the regulation for ATMPs and up to November 2025, 28 ATMPs have been authorised in

the EU. Of these, nine have a withdrawn or an expired marketing authorisation (MA), leaving 19 products on the market. Of these, 18 ATMPs have submitted a reimbursement application to AIFA. Overall, 15/18 (83.3 %) of these ATMPs have an orphan designation, and 12/18 (66.6%) underwent the PRIME program at the EMA, while none of them had an accelerated assessment. The EMA assessment, which took – on average – 526 days, resulted in 11 full approvals (8 of which were OMPs), 5 conditional approvals (all for OMPs), 2 approvals in exceptional circumstances (both for OMPs).

So far, AIFA has assessed, appraised and classified 17 of the ATMPs with a submitted P&R dossier, with a positive reimbursement decision issued for 15/17 (88,2 %). This means that 79 % of all ATMPs authorised in the EU are reimbursed for patients in Italy (15/19). A total of 13/15 (86,6 %) reimbursed ATMPs were considered innovative for their first authorised indications (Table 3). With respect to the seven extensions of indications authorised by EMA for ATMPs in the last few years, four have already been evaluated, and two were considered innovative indications, while three more are currently under assessment.

Once AIFA officially issues the reimbursement decision, Regions need to act to make the products available to hospitals and patients. By the end of 2024, 12 ATMPs had already been reimbursed, and 11 of them had been purchased through the NHS to treat patients. The median time to first purchase of an ATMP by the NHS was 217 days after the resolution publication in the OIJ (mean 340 days), ranging from 4 to 1342 when analysing data at the single product and regional level.

It is worth noticing that this wide range of time to patient access is not only due to administrative regional differences, but also to several intertwined factors. The epidemiology of these rare diseases creates a heterogeneous pattern of need, where larger regions with a higher number of inhabitants will also have a higher number of prevalent and incident patients that seek treatment.

Additionally, the possibility of administering these very peculiar products only in specialised centres further biases this type of time to access analysis. In Italy, products like CAR-Ts are administered in centres that are identified by the regions based on specific criteria. Furthermore, the identified centres need to be subsequently qualified by the MAH, as defined by their Risk management plan. This double safety procedure, which is mandatory before activation of a CAR-T centre, is warranted to delay patient access after the reimbursement decision.

Since 2016, ATMPs have seen growth in Italy in terms of expenditure.[15] In 2024, 580 patients were treated with ATMPs reimbursed by the Italian NHS, costing 194.5 million euros, which is approximately 6.9 ‰ of the national pharmaceutical expenditure. In 2024, CAR-Ts were used in 93.6 % of treatments involving ATMPs (543 CAR-T treatments out of 580), costing 145.5 million euros to the NHS. In comparison, all other ATMPs – non-CAR-T ex vivo gene therapies, in vivo gene therapies, somatic cell therapies, and tissue engineering therapies – were used for 37 treatments, totalling 49 million euros.[16]

Conclusions

We observed that almost all ATMPs approved by the EMA are reimbursed by AIFA, and reported a growing expenditure on such therapies over the past few years. Such trends pose significant challenges for the national health system, which is called to make such technologies available to the population while managing the uncertainties brought by immature evidence.

To close this gap, national incentives have been implemented, with the specific aim of recognising the therapeutic benefits of treatments for unmet medical needs, parti-

cularly in rare diseases, thus speeding up access in keeping with clinical value. Furthermore, AIFA has implemented web-based registries that ensure appropriate eligibility and enhance monitoring of patient outcomes. All these initiatives intend to promote timely, cost-effective access to promising therapeutic options while monitoring their application to connect clinical trial data with real-world clinical practice.

While further research from AIFA registries will tell us how these technologies are used in real-life settings, we should also be aware of the regional variability, which may represent the bottleneck to access.

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EU-authorized ATMPs with a P&R dossier submitted to AIFA (n=18), up to 15th November 2025

N.	Brand name	Active substance	ATMP	CAR-T	Clinial condition
1	Holoclar	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Tissue engineered	No	Moderate to severe limbal stem cell deficiency
2	Strimvelis	An autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine	Ex vivo gene therapy	No	Severe combined immunodeficiency due to ADA deficiency (ADA-SCID)
3	Spherox	Spheroids of human autologous matrix-associated chondrocytes for implantation suspended in isotonic sodium chloride solution	Tissue engineered	No	Symptomatic articular cartilage defects of the knee
4	Kymriah	Tisagenlecleucel	Ex vivo gene therapy	Yes	- Relapsed or refractory B-ALL - Relapsed or refractory DLBCL
5	Yescarta	Axicabtagene ciloleucel	Ex vivo gene therapy	Yes	Relapsed or refractory DLBCL and PMBCL
6	Luxturna	Voretigene neparvovec	In vivo gene therapy	No	Inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations
7	Zolgensma	Onasemnogene abeparvovec	In vivo gene therapy	No	5q spinal muscular atrophy (SMA) with up to three copies of the SMN2 gene
8	Tecartus	Brexucabtagene autoleucel	Ex vivo gene therapy	Yes	Relapsed or refractory mantle cell lymphoma (MCL)
9	Libmeldy	Atidarsagene autotemcel	Ex vivo gene therapy	No	Metachromatic leukodystrophy (MLD)
10	Abecma	Idecabtagene vicleucel	Ex vivo gene therapy	Yes	Relapsed and refractory multiple myeloma
11	Upstaza	Eladocagene exuparvovec	In vivo gene therapy	No	Severe aromatic L-amino acid decarboxylase deficiency
12	Carvykti	Ciltacabtagene autoleucel	Ex vivo gene therapy	Yes	Relapsed and refractory multiple myeloma
13	Breyanzi	Lisocabtagene maraleucel	Ex vivo gene therapy	Yes	Relapsed or refractory DLBCL, HGBCL, PMBCL and FL3B
14	Roctavian	Valoctocogene roxaparvovec	In vivo gene therapy	No	Severe haemophilia A
15	Ebvallo	Tabelecleucel	Somatic stem cell therapy	No	Relapsed or refractory EBV positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have
16	Hemgenix	Etranacogene dezaparvovec	In vivo gene therapy	No	Severe and moderately severe Haemophilia B
17	Casgevy	Exagamglogene autotemcel	Ex vivo gene therapy	No	- Transfusion dependent β thalassemia - Severe sickle cell disease
18	Vyjuvek	Beremagene geperpavec	In vivo gene therapy	No	Wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene, from

Abbreviations: CMA conditional marketing authorization, UEC under exceptional circumstances, DLBCL diffuse large B-cell lymphoma, PMBCL primary mediastinal B-cell lymphoma, HGBL high grade lymphoma, ALL acute lymphoblastic leukemia, FL3b follicylar lymphoma type 3b, EBV Epstein-Barr virus

Source: AIFA

Table 3: AIFA has assessed, appraised and classified 17 of the ATMPs with a submitted P&R dossier, with a positive reimbursement decision issued for 15/17. This means that 79% of all ATMPs authorised in the EU are reimbursed for patients in Italy (15/19). A total of 13/15 reimbursed ATMPs were considered innovative for their first authorised indications.

Oncologic condition	Orphan drug	EC authorization		Innovativeness	Publication of the reimbursement resolution in the OG	AIFA decision
No	Yes	CMA	17/02/2015	Yes (expired)	24/02/2017	Reimbursed
No	Yes	Standard	26/05/2016	No	01/08/2016	Reimbursed
No	No	Standard	10/07/2017	na	26/11/2021	Not reimbursed
Yes	Yes	Standard	23/08/2018	Yes (expired)	12/08/2019	Reimbursed
Yes	Yes	Standard	23/08/2018	Yes (expired)	11/11/2019	Reimbursed
No	Yes	Standard	22/11/2018	Yes (expired)	09/01/2021	Reimbursed
No	Yes	CMA	18/05/2020	Yes (expired)	13/03/2021	Reimbursed
Yes	Yes	CMA	14/12/2020	Yes (expired)	11/03/2022	Reimbursed
No	Yes	Standard	17/12/2020	Yes (expired)	07/04/2022	Reimbursed
Yes	Yes	CMA	18/08/2021	Conditioned	08/02/2024	Reimbursed
No	Yes	UEC	18/07/2022	Yes	04/12/2023	Reimbursed
Yes	Yes	CMA	25/05/2022	na	24/03/2025	Not reimburesd
Yes	No	Standard	04/04/2022	Yes (expired)	08/02/2024	Reimbursed
No	Yes	CMA	24/08/2022	Conditioned	22/01/2024	Reimbursed
Yes	Yes	UEC	16/12/2022	No	13/03/2025	Reimbursed
No	Yes	CMA	20/02/2023	Yes	03/09/2025	Reimbursed
No	Yes	CMA	09/02/2024	Yes	07/10/2025	Reimbursed
No	Yes	Standard	23/04/2025	na	na	Under assessment

Broadly accepted standards for studies beyond RCTs are only gradually emerging

By Florian Staeck

Due to the increasing number of approvals based on single-arm pivotal trials, the evidence required for early benefit assessment, in which new pharmaceuticals are compared with the current standard of care, is often lacking. This applies in particular to rare diseases and to Advanced Therapy Medicinal Products (ATMPs).

Although the Federal Government has committed itself to a learning healthcare model through the National Genomic Medicine Strategy (genomDE), intended to meaningfully link research and clinical care, the prospective plans also include piloting the manufacture and use of ATMPs in so-called ATMP Innovation Centres. At the same time, it was reported that reimbursement requests for ATMPs are not infrequently rejected by statutory health insurers, often following lengthy consultations with the Medical Service. To date, the dominant ATMP product classes have been gene therapies for rare diseases and CAR T-cell therapies in haematology.

Against this backdrop, participants at the Interdisciplinary Platform on Benefit Assessment discussed the perspectives and challenges associated with the topic in Berlin on 26–27 September 2025 under the title ATMPs and Rare Diseases: Innovation in Research, Data Collection and Benefit Assessment. Different views emerged during the debate:

a. Pharmaceutical manufacturers argued that the specific characteristics of these novel therapeutic approaches are insufficiently reflected in the current AMNOG framework. They also criticised the lack of a balanced assessment of the feasibility and appropriateness of RCTs in the context of benefit assessment.

Instead, the focus, they maintained, should be on taking the best available evidence into account. To this end, the legal framework and the Pharmaceutical Benefit Assessment Ordinance would need to be amended accordingly. This would apply in particular to the acceptance of real-world data. In this context, the evidentiary requirements for routine practice data collection were described as excessively high.

It was further criticised that there is no clearly defined decision-making framework and that, in cases of doubt, the Federal Joint Committee (G-BA) resorts to case-by-case decisions. The „ground" provided in G-BA decisions, it was argued, generally do not make sufficiently clear to what extent the specific therapeutic situation has been taken into account. It was also noted that recognition of additional benefit for ATMPs varies considerably across EU Member States.

b. In response, it was argued that the G-BA does in fact routinely assess data beyond randomised controlled trials (RCTs). Within the framework of benefit assessment, the specific therapeutic context is always discussed. There is no categorical rejection of alternative study designs within the G-BA; however, it was stated that fixed criteria for defining „special" therapeutic situations cannot be specified.

At the same time, it was acknowledged that, in many clinical studies on ATMPs to date, data on quality of life and morbidity have not been assessable, predominantly because the available data did not allow for quantification. This was also attributed to the lack of a research data infrastructure in Germany that would enable suitable indirect comparisons to be submitted for benefit assessment. Data from registries, it was noted, often do not permit systematic identification of confounding variables or the collection of all required baseline characteristics. In addition, endpoints are frequently not defined in a uniform manner. It was viewed positively that the Medical Research Act mandates the Federal Ministry of Health (BMG) to outline a framework for an ATMP registry by 2027. The necessary

preparatory work, it was reported, is being supported by a project funded through the Innovation Fund.

According to participants, the potential and opportunities arising from linking different data sources can be illustrated by the example of cancer registries. The Act on the Consolidation of Cancer Registry Data, adopted in 2021, created the possibility of linking clinical cancer registry data with other data sources. Such a joint platform would create potential to use existing data for clinical guidelines, registry-based studies or benefit assessments, in the sense of an „evidence-informed, ‚learning' healthcare system," it was stated. Within this framework, data would not be centralised but rather linked on a case-by-case basis. This approach, the conclusion held, offers the opportunity to enhance transparency in healthcare delivery through real-world data.

Against the backdrop of the differing positions and assessments outlined above, participants focused their discussion in particular on the following points:

Perspective of the regulatory authorities on ATMP:
The Medical Research Act has shortened the processing timelines with regard to ATMP. The procedure may now take a total of 109 days, and the authority must issue its decision within 26 days. Cooperation between the Paul-Ehrlich-Institute (PEI) and the Federal Institute for Drugs and Medical Devices (BfArM) is envisaged, including with the aim of assuming the role of (co-)rapporteur in a greater number of procedures. In doing so, the respective areas of expertise of the two federal authorities are to be used in a complementary manner.

It was reported that the responsible department at the PEI is currently registering an increasing number of requests for scientific advice, a trend that is likely to continue in view of the growing number of centralised marketing authorisation procedures.

The Medical Research Act has mandated the PEI to issue recommendations on the interpretation of Good Manufacturing Practice (GMP). The authority has complied with this mandate by publishing GMP guidelines for ATMP. Overall, however, ATMP constitute very heterogeneous products. Consequently, „guidelines" can only be developed to a limited extent.

Challenges and opportunities in dealing with registry data:
Existing indication-specific registries are, in principle, suitable to serve as a primary data source for routine practice data collection. However, it was noted that substantial adjustments would be required, as the data structures in many registries are not designed to meet the requirements of AMNOG. This may concern, for example, harmonised reporting and data collection time points. In an RCT, defining the start of observation does not pose a problem. In the context of routine practice data collection, by contrast, a variety of different treatment concepts are often encountered.

The collection of patient-reported outcomes (PROs) is, in many cases, not yet implemented in registries and, it was argued, would not be meaningful if confined to the registry setting alone. One potential solution could lie in the use of digital tools to facilitate data collection for patients.

Participants pointed out that maintaining a registry with high-quality data entails considerable costs, while the long-term financing of such infrastructures is often not secured. The example of the haemophilia registry in Germany illustrates the long-term commitment required to establish a registry capable of generating high-quality data.

Building such an infrastructure in the first place was described as a „Herculean task". It was further stated that at-

tempting to establish a registry-based RCT solely for the purpose of benefit assessment under AMNOG would, in any event, be doomed to fail.

With regard to the current draft legislation on medical registries, participants expressed hope that the legislator might facilitate data collection in specific indications through an appropriate registry data infrastructure. This should, they argued, be accompanied by advisory support for registry operators on regulatory HTA issues provided by the Federal Joint Committee and the competent federal authorities.

A recent ruling of the European Court of Justice was regarded as a positive development. In September 2025 (Case C-413/23 P), the Court held that pseudonymised data are, in practical terms, to be treated as anonymised data. Previously, the linking of datasets had repeatedly been impeded by data protection authorities on the grounds that pseudonymised data should be considered personal data.

Weaknesses and need for reform of routine practice data collection:

Participants drew a predominantly negative conclusion regarding the instrument of routine practice data collection. Instead of the nine to ten procedures per year that the legislator had anticipated at the outset, only five such procedures are currently ongoing. In 69 cases, it had previously been explored whether routine practice data collection might be appropriate.

Participants recalled that the German Advisory Council on Health and Care had described routine practice data collection ineffective in its current form. According to this assessment, the instrument neither generates system-relevant savings nor sustainably improves the evidence base. Originally, routine practice data collection was intended to prevent the reimbursement amount from remaining permanently at the same level in cases where sufficient evidence of additional benefit was lacking. It was argued that this objective, too, has not been achieved.

In explaining this critical assessment, reference was made, first, to the lengthy duration of the procedure, which – from candidate selection to benefit assessment – may take six to eight years. Secondly, questions were raised as to the relevance of such data by the time they become available. For example, the first assessment of osmogene abeparvovec (Zolgensma®) based on routine practice data collection is scheduled for 2027. Since February 2022, however, the gene therapy has only been permitted to be administered by physicians participating in the registry study and documenting the required data.

It was further pointed out that the G-BA cannot compel cooperation from the respective pharmaceutical manufacturer, nor can it impose requirements on registry operators regarding data sources. In addition, methodological challenges were highlighted, as routine practice data collection is considered sufficiently sensitive only to detect very large effect differences in patient-relevant endpoints.

Regulatory alternatives for dealing with data uncertainty:

The „new" discussion called for by some participants on how to address uncertainty in regulatory approval and benefit assessment was only partially discernible at the platform meeting. Starting from the current status quo, some participants advocated in particular for improving the quality of planned RCTs so that they could be used not only for the regulatory approval process but also for benefit assessment or the EU HTA procedure.

However, the debate remained conceptually vague regarding alternatives in cases where an RCT proves infeasible. It was suggested that comparative real-world data

should be collected prospectively in parallel with the approval study. At the same time, it was emphasised that the current regulatory framework does not provide sufficient incentives to generate suitable data in advance for adjusted indirect comparisons. Other participants proposed „joint advice" from regulatory and HTA authorities as a further option, whereby guidance could be provided on the conduct of an RCT or an alternative study design. It was cautioned, however, that such advice would also need to be robust and reliable in the context of the subsequent benefit assessment.

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ATMP & Orphan Diseases: Data sources beyond RCTs

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